

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 December 2000 (21.12.2000)

PCT

(10) International Publication Number
WO 00/76961 A1

(51) International Patent Classification⁷: C07C 311/16,
311/29, C07D 317/46, A61K 31/36, A61P 31/18, A61K
31/352, C07D 493/04

(21) International Application Number: PCT/US00/15781

(22) International Filing Date: 8 June 2000 (08.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/139,070 11 June 1999 (11.06.1999) US
60/190,211 17 March 2000 (17.03.2000) US

(71) Applicant (for all designated States except US): VERTEX
PHARMACEUTICALS INCORPORATED [US/US];
130 Waverly Street, Cambridge, MA 02139-4242 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): HALE, Michael,
Robin [US/US]; 42 Sunset Road, Bedford, MA 01730
(US). TUNG, Roger [US/US]; 14 Thoreau Circle, Beverly,
MA 01915 (US). PRICE, Stephen [GB/GB]; 25 Eskdale
Road, Stoke Mandeville, Aylesbury, Bucks HP22 5UJ
(GB). WILKES, Robin, David [GB/GB]; 7 Swarbourne
Close, Didcot, Oxon OX11 7UL (GB). SCHAIRER,
Wayne, Carl [US/US]; 135 Milk Street, Westborough,
MA 01581 (US). JARVIS, Ashley, Nicholas [GB/GB];
56 West Street, Osney, Oxford OX2 0BH (GB). SPAL-
TENSTEIN, Andrew [US/US]; 4105 Brewster Drive,
Raleigh, NC 27606 (US). FURFINE, Eric, Steven
[US/US]; 4133 Livingstone Place, Durham, NC 27707

(US). SAMANO, Vicente [MX/US]; 410 Englewood
Drive, Chapel Hill, NC 27514 (US). KALDOR, Istvan
[HU/US]; 7 Bonham Court, Durham, NC 27703 (US).
MILLER, John, Franklin [US/US]; 310 Continental
Drive, Durham, NC 27712 (US). BRIEGER, Michael,
Stephen [US/US]; 2110 Paces Forest Court #421, Raleigh,
NC 27612 (US).

(74) Agents: HALEY, James, F., Jr.; Fish & Neave, 1251 Av-
enue of the Americas, New York, NY 10020 et al. (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE,
DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO,
NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments.

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.



WO 00/76961 A1

(54) Title: INHIBITORS OF ASPARTYL PROTEASE

(57) Abstract: The present invention relates to a novel class of sulfonamides which are aspartyl protease inhibitors. In one embodiment, this invention relates to a novel class of HIV aspartyl protease inhibitors characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting HIV-1 and HIV-2 protease activity and consequently, may be advantageously used as anti-viral agents against the HIV-1 and HIV-2 viruses. This invention also relates to methods for inhibiting the activity of HIV aspartyl protease using the compounds of this invention and methods for screening compounds for anti-HIV activity.

INHIBITORS OF ASPARTYL PROTEASE

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a novel class of sulfonamides which are aspartyl protease inhibitors. In one embodiment, this invention relates to a novel class of HIV aspartyl protease inhibitors characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting HIV-1 and HIV-2 protease activity and consequently, may be advantageously used as anti-viral agents against the HIV-1 and HIV-2 viruses. This invention also relates to methods for inhibiting the activity of HIV aspartyl protease using the compounds of this invention and methods for screening compounds for anti-HIV activity.

BACKGROUND OF THE INVENTION

The human immunodeficiency virus ("HIV") is the causative agent for acquired immunodeficiency syndrome ("AIDS") -- a disease characterized by the destruction of the immune system, particularly of CD4⁺ T-cells, with

-2-

attendant susceptibility to opportunistic infections -- and its precursor AIDS-related complex ("ARC") -- a syndrome characterized by symptoms such as persistent generalized lymphadenopathy, fever and weight loss.

5 As in the case of several other retroviruses, HIV encodes the production of a protease which carries out post-translational cleavage of precursor polypeptides in a process necessary for the formation of infectious virions (S. Crawford et al., "A Deletion Mutation in the
10 5' Part of the pol Gene of Moloney Murine Leukemia Virus Blocks Proteolytic Processing of the gag and pol Polyproteins", J. Virol., 53, p. 899 (1985)). These gene products include pol, which encodes the virion RNA-dependent DNA polymerase (reverse transcriptase), an
15 endonuclease, HIV protease, and gag, which encodes the core-proteins of the virion (H. Toh et al., "Close Structural Resemblance Between Putative Polymerase of a Drosophila Transposable Genetic Element 17.6 and pol gene product of Moloney Murine Leukemia Virus", EMBO J., 4, p. 1267 (1985); L.H. Pearl et al., "A Structural Model for the Retroviral Proteases", Nature, pp. 329-351 (1987); M.D. Power et al., "Nucleotide Sequence of SRV-1, a Type D Simian Acquired Immune Deficiency Syndrome Retrovirus", Science, 231, p. 1567 (1986)).

25 A number of synthetic anti-viral agents have been designed to target various stages in the replication cycle of HIV. These agents include compounds which block viral binding to CD4⁺ T-lymphocytes (for example, soluble CD4), and compounds which interfere with viral
30 replication by inhibiting viral reverse transcriptase (for example, didanosine and zidovudine (AZT)) and inhibit integration of viral DNA into cellular DNA (M.S. Hirsh and R.T. D'Aquila, "Therapy for Human

-3-

Immunodeficiency Virus Infection", N.Eng.J.Med., 328, p. 1686 (1993)). However, such agents, which are directed primarily to early stages of viral replication, do not prevent the production of infectious virions in chronically infected cells. Furthermore, administration of some of these agents in effective amounts has led to cell-toxicity and unwanted side effects, such as anemia and bone marrow suppression.

More recently, the focus of anti-viral drug design has been to create compounds which inhibit the formation of infectious virions by interfering with the processing of viral polyprotein precursors. Processing of these precursor proteins requires the action of virus-encoded proteases which are essential for replication (Kohl, N.E. et al. "Active HIV Protease is Required for Viral Infectivity" Proc. Natl. Acad. Sci. USA, 85, p. 4686 (1988)). The anti-viral potential of HIV protease inhibition has been demonstrated using peptidyl inhibitors.

More recently several small molecule protease inhibitors have become available for the treatment of HIV infections. Among these is the sulfonamide-containing molecule, Agenerase® (amprenavir). Agenerase® is described in United States patent 5,585,397. Other sulfonamide inhibitors of aspartyl protease are described in United States patents 5,691,372, 5,510,388, 5,521,219, 5,639,769, 5,714,605, 5,744,481, 5,786,483, 5,830,897 and 5,843,946.

Because HIV-infected patients often develop resistance to particular protease inhibitors, the need still exists for additional compounds that can effectively inhibit the action of aspartyl proteases, particularly HIV protease, for use as agents for

-4-

preventing and treating chronic and acute viral infections. Moreover, there is also a need for compounds that can effectively inhibit the action of HIV mutants which are resistant to conventional protease inhibitors.

5

SUMMARY OF THE INVENTION

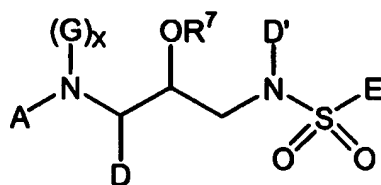
The present invention provides a novel class of compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of aspartyl proteases, in particular, HIV aspartyl protease. These compounds can be used alone or in combination with other therapeutic or prophylactic agents, such as anti-virals, antibiotics, immunomodulators or vaccines, for the treatment or prophylaxis of viral infection.

According to a preferred embodiment, the compounds of this invention are capable of inhibiting HIV viral replication in human CD₄⁺ T-cells. These compounds are useful as therapeutic and prophylactic agents to treat or prevent infection by HIV-1 and related viruses which may result in asymptomatic infection, AIDS-related complex ("ARC"), acquired immunodeficiency syndrome ("AIDS"), or similar disease of the immune system.

According to another preferred embodiment, the compounds of this invention are useful as therapeutic and prophylactic agents to treat or prevent infection by HIV mutants.

It is a principal object of this invention to provide a novel class of sulfonamides which are aspartyl protease inhibitors, and particularly, HIV aspartyl protease inhibitors. The novel sulfonamides of this invention are those of formula I:

-5-



(I)

and pharmaceutically acceptable salts thereof;
wherein:

- A is selected from H; Ht; $-R^1\text{-Ht}$; $-R^1\text{-C}_1\text{-C}_6$ alkyl,
5 which is optionally substituted with one or more groups independently selected from hydroxy, $-\text{CN}$, $\text{C}_1\text{-C}_4$ alkoxy, Ht, $-\text{O-Ht}$, $-\text{NR}^2\text{-Ht}$, $-\text{NR}^2\text{-CO-N(R}^2\text{)}_2$, $-\text{SO}_2\text{-N(R}^2\text{)}_2$, $-\text{SO}_2\text{-R}^2$ or $-\text{CO-N(R}^2\text{)}_2$; $-R^1\text{-C}_2\text{-C}_6$ alkenyl, which is optionally substituted with one or more groups independently
10 selected from hydroxy, $\text{C}_1\text{-C}_4$ alkoxy, Ht, $-\text{O-Ht}$, $-\text{NR}^2\text{-CO-N(R}^2\text{)}_2$ or $-\text{CO-N(R}^2\text{)}_2$; or R^7 ;
- each R^1 is independently selected from $-\text{C(O)-}$, $-\text{S(O)}_2\text{-}$, $-\text{C(O)-C(O)-}$, $-\text{O-C(O)-}$, $-\text{O-S(O)}_2\text{-}$, $-\text{NR}^2\text{-}$, $-\text{NR}^2\text{-S(O)}_2\text{-}$, $-\text{NR}^2\text{-C(O)-}$ or $-\text{NR}^2\text{-C(O)-C(O)-}$;
- 15 each Ht is independently selected from $\text{C}_3\text{-C}_7$ cycloalkyl; $\text{C}_5\text{-C}_7$ cycloalkenyl; $\text{C}_6\text{-C}_{14}$ aryl; or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, $\text{N(R}^2\text{)}$, O, S and S(O)_n ; wherein said aryl or said heterocycle is optionally
20 fused to Q; and wherein any member of said Ht is optionally substituted with one or more substituents independently selected from oxo, $-\text{OR}^2$, SR^2 , $-\text{R}^2$, $-\text{N(R}^2\text{)(R}^2\text{)}$, $-\text{R}^2\text{-OH}$, $-\text{CN}$, $-\text{CO}_2\text{R}^2$, $-\text{C(O)-N(R}^2\text{)}_2$, $-\text{S(O)}_2\text{-N(R}^2\text{)}_2$, $-\text{N(R}^2\text{)-C(O)-R}^2$, $-\text{N(R}^2\text{)-C(O)O-R}^2$, $-\text{C(O)-R}^2$, $-\text{S(O)}_n\text{-R}^2$, $-\text{OCF}_3$,
25 $-\text{S(O)}_n\text{-Q}$, methylenedioxy, $-\text{N(R}^2\text{)-S(O)}_2\text{(R}^2\text{)}$, halo, $-\text{CF}_3$, $-\text{NO}_2$, Q, $-\text{OQ}$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{R}^7$, $-\text{N(R}^2\text{)(R}^7\text{)}$ or $-\text{N(R}^7\text{)}_2$;
- each R^2 is independently selected from H, or $\text{C}_1\text{-C}_4$ alkyl optionally substituted with a 3-7 membered saturated, partially saturated or unsaturated carbocyclic
30 ring system; or a 5-7 membered saturated, partially

-6-

saturated or unsaturated heterocyclic ring containing one or more heteroatoms selected from O, N, S, $S(O)_n$ or $N(R^{33})$; wherein any of said ring systems or $N(R^{33})$ is optionally substituted with 1 to 4 substituents

5 independently selected from $-X'-Y'$, $-O$ -arylalkyl, $-S$ -arylalkyl, $-N(Y')_2$, $-N(H)$ -arylalkyl, $-N(C_1-C_4$ alkyl)-arylalkyl, oxo, $-O-(C_1-C_4$ alkyl), OH, C_1-C_4 alkyl, $-SO_2H$, $-SO_2-(C_1-C_4$ alkyl), $-SO_2-NH_2$, $-SO_2-NH(C_1-C_4$ alkyl), $-SO_2-N(C_1-C_4$ alkyl) $_2$, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$

10 alkyl) $_2$, $-NH-C(O)H$, $-N(C_1-C_4$ alkyl)- $C(O)H$, $-NH-C(O)-C_1-C_4$ alkyl, $-C_1-C_4$ alkyl-OH, -OH, -CN, $-C(O)OH$, $-C(O)O-C_1-C_4$ alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_1-C_4$ alkyl), $-C(O)-N(C_1-C_4$ alkyl) $_2$, halo or $-CF_3$;

X' is $-O-$, $-S-$, $-NH-$, $-NHC(O)-$, $-NHC(O)O-$, $-NHSO_2-$,
 15 or $-N(C_1-C_4)alkyl-$;

Y' is C_1-C_{15} alkyl, C_2-C_{15} alkenyl or alkynyl, wherein one to five carbon atoms in Y are optionally substituted with C_3-C_7 cycloalkyl or C_5-C_6 cycloalkenyl, C_6-C_{14} aryl or a 5-7 membered saturated or unsaturated heterocycle,
 20 containing one or more heteroatoms selected from N, NH, O, S and $S(O)_n$;

each R^3 is independently selected from H, Ht, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or C_5-C_6 cycloalkenyl; wherein any member of said R^3 , except
 25 H, is optionally substituted with one or more substituents selected from $-OR^2$, $-C(O)-N(R^2)_2$, $-S(O)_n-N(R^2)_2$, $-N(R^2)_2$, $-N(R^2)-C(O)O(R^2)$, $-N(R^2)-C(O)N(R^2)_2$, $-N(R^2)-C(O)-R^2$, Ht, -CN, $-SR^2$, $-C(O)OR^2$, $N(R^2)-C(O)-R^2$;

each R^{33} is selected from H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or C_5-C_6 cycloalkenyl, C_6-C_{14} aryl or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, NH, O, S and $S(O)_n$;

30

-7-

each n is independently 1 or 2;

G, when present, is selected from H, R⁷ or C₁-C₄ alkyl, or, when G is C₁-C₄ alkyl, G and R⁷ are bound to one another either directly or through a C₁-C₃ linker to form
5 a heterocyclic ring; or

when G is not present (i.e., when x in (G)_x is 0), then the nitrogen to which G is attached is bound directly to the R⁷ group in -OR⁷ with the concomitant displacement of one -ZM group from R⁷;

10 D is selected from C₁-C₆ alkyl which is substituted with Q, which is optionally substituted with one or more groups selected from C₃-C₆ cycloalkyl, -R³, -O-Q or Q; C₂-C₄ alkenyl which is substituted with Q, which is optionally substituted with one or more groups selected
15 from -OR², -S-Ht, -R³, -O-Q or Q; C₃-C₆ cycloalkyl, which is optionally substituted with or fused to Q; or C₅-C₆ cycloalkenyl, which is optionally substituted with or fused to Q;

each Q is independently selected from a 3-7 membered
20 saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one or more heteroatoms selected from O, N, S, S(O)_n or N(R²); wherein Q contains one substituent selected from -OR², -
25 OR⁸, -O-arylalkyl, -SR⁸, -S-arylalkyl, -N(R²)R⁸, -N(R²)-arylalkyl and may be optionally substituted with one or more additional substituents independently selected from oxo, -OR⁸, -O-arylalkyl -SR⁸, -S-arylalkyl, -N(R²)R⁸, -N(R²)-arylalkyl, -OR², -R², -SO₂R², -SO₂-N(R²)₂, -N(R²)₂,
30 -N(R²)-C(O)-R², -OH, (C₁-C₄)-OH, -CN, -CO₂R², -C(O)-N(R²)₂, halo or -CF₃;

each R⁸ is independently selected from Ht, -C₁-C₁₅ branched or straight chain alkyl, alkenyl or alkynyl

wherein one to five carbon atoms in said alkyl, alkenyl or alkynyl are independently replaced by W, or wherein one to five carbon atoms in said alkyl, alkenyl or alkynyl are substituted with Ht; and wherein R⁸ is

5 additionally and optionally substituted with one or more groups independently selected from -OH, -S(C₁-C₆ alkyl), -CN, -CF₃, -N(R²)₂, halo, -C₁-C₄-alkyl, -C₁-C₄-alkoxy; -Ht; -O-Ht; -NR²-CO-N(R²)₂; -CO-N(R²)₂; -R¹-C₂-C₆ alkenyl, which is optionally substituted with one or more groups

10 independently selected from hydroxy, C₁-C₄ alkoxy, Ht, -O-Ht, -NR²-CO-N(R²)₂ or -CO-N(R²)₂; or R⁷;

wherein W is -O-, -NR²-, -S-, -C(O)-, -C(S)-, -C(=NR²)-, -S(O)₂-, -NR²-S(O)₂-, -S(O)₂-NR²-, -NR²-C(O)O-, -O-C(O)NR²-, -NR²-C(O)NR²-, -NR²-C(S)NR²-, -CONR², -NR²C(O)-, -C(S)NR², -NR²C(S)-, -NR²-C(=N-CN)-NR²-, -NR²C(=N-CN)O- or -C(O)O-;

15

D' is selected from C₁-C₁₅ alkyl, C₁-C₁₅ alkoxy, C₂-C₁₅ alkenyl, C₂-C₁₅ alkenyloxy, C₂-C₁₅ alkynyl, or C₂-C₁₅ alkynyloxy, wherein D' optionally comprises one or more

20 substituents independently selected from Ht, oxo, halo, -CF₃, -OCF₃, -NO₂, azido, -SH, -SR³, -N(R³)-N(R³)₂, -O-N(R³)₂, -(R³)N-O-(R³), -N(R³)₂, -CN, -CO₂R³, -C(O)-N(R³)₂, -S(O)_n-N(R³)₂, -N(R³)-C(O)-R³, -N(R³)-C(O)-N(R³)₂, -C(O)-R³, -S(O)_n-R³, -N(R³)-S(O)_n(R³), -N(R³)-S(O)_n-N(R³)₂, -S-NR³-C(O)R³, -C(S)N(R³)₂, -C(S)R³, -NR³-C(O)OR³, -O-C(O)OR³, -O-C(O)N(R³)₂, -NR³-C(S)R³, =N-OH, =N-OR³, =N-N(R³)₂, =NR³, =NNR³C(O)N(R³)₂, =NNR³C(O)OR³, =NNR³S(O)_n-N(R³)₂, -NR³-C(S)OR³, -NR³-C(S)N(R³)₂, -NR³-C[=N(R³)]-N(R³)₂, -N(R³)-C[=N-NO₂]-N(R³)₂, -N(R³)-C[=N-NO₂]-OR³, -OC(O)R³, -OC(S)R³, -OC(O)N(R³)₂, -C(O)N(R³)-N(R³)₂, -N(R³)-N(R³)C(O)R³, -N(R³)-OC(O)R³, -N(R³)-OC(O)R³, -N(R³)-OC(O)R³, -OC(S)N(R³)₂, -OC(S)N(R³)(R³), or -PO₃-R³;

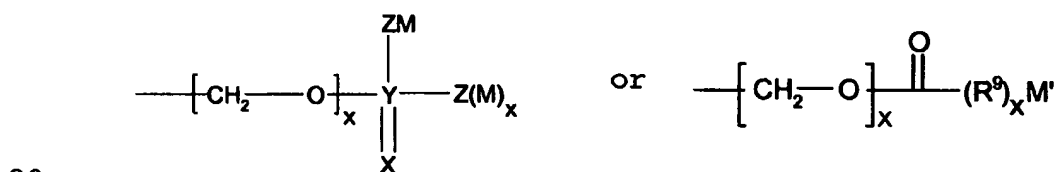
25

30

E is selected from Ht; O-Ht; Ht-Ht; Ht fused with Ht; -O-R³; -N(R²)(R³); -N(R²)-Ht; C₁-C₆ alkyl, which is optionally substituted with one or more groups selected from R⁴ or Ht; C₂-C₆ alkenyl, which is optionally substituted with one or more groups selected from R⁴ or Ht; C₃-C₆ saturated carbocycle, which is optionally substituted with one or more groups selected from R⁴ or Ht; or C₅-C₆ unsaturated carbocycle, which is optionally substituted with one or more groups selected from R⁴ or Ht;

each R⁴ is independently selected from -R², -OR², -OR³, -SR², -SOR², -SO₂R², -CO₂R², -OC(O)-R², -C(O)-N(R²)₂, -C(O)-NR²(OR²), -S(O)₂-N(R²)₂, halo, -NR²-C(O)-R², -NR²-OR², -N(R²)₂ or -CN;

each R⁷ is independently selected from hydrogen,



wherein each M is independently selected from H, Li, Na, K, Mg, Ca, Ba, -N(R²)₄, C₁-C₁₂-alkyl, C₂-C₁₂-alkenyl, or -R⁶; wherein 1 to 4 -CH₂ radicals of the alkyl or alkenyl group, other than the -CH₂ that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, S(O), S(O₂), or N(R²); and wherein any hydrogen in said alkyl, alkenyl or R⁶ is optionally replaced with a substituent selected from oxo, -C₁-C₄ alkyl, -N(R²)₂, -N(R²)₃, -OH, -O-(C₁-C₄ alkyl), -CN, -C(O)OR², -C(O)-N(R²)₂, S(O)₂-N(R²)₂, -N(R²)-C(O)-R₂, C(O)R², -S(O)_n-R², -OCF₃, -S(O)_n-R⁶, -N(R²)-S(O)₂(R²), halo, -CF₃, or -NO₂;

-10-

- M' is H, C₁-C₁₂-alkyl, C₂-C₁₂-alkenyl, or -R⁶; wherein 1 to 4 -CH₂ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from O, S, S(O), S(O)₂, or N(R²); and wherein any hydrogen in said alkyl, alkenyl or R⁶ is optionally replaced with a substituent selected from oxo, -OR², -C₁-C₄ alkyl, -N(R²)₂, N(R²)₃, -OH, -O-(C₁-C₄ alkyl), -CN, -C(O)OR², -C(O)-N(R²)₂, -S(O)₂-N(R²)₂, -N(R²)-C(O)-R₂, -C(O)R², -S(O)_n-R², -OCF₃, -S(O)_n-R⁶, -N(R²)-S(O)₂(R²), halo, -CF₃, or -NO₂;
- 10 x is 0 or 1;
 Z is O, S, N(R²)₂, or, when M is not present, H.
 Y is P or S;
 X is O or S; and
 R⁹ is C(R²)₂, O or N(R²); and wherein when Y is S, Z
15 is not S; and
- R⁶ is a 5-6 membered saturated, partially saturated or unsaturated carbocyclic or heterocyclic ring system, or an 8-10 membered saturated, partially saturated or unsaturated bicyclic ring system; wherein any of said
20 heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, S(O)_n or N(R²); and wherein any of said ring systems optionally contains 1 to 4 substituents independently selected from -OH, -C₁-C₄ alkyl, -O-(C₁-C₄ alkyl) or -O-C(O)-(C₁-C₄ alkyl).
- 25 It is also an object of this invention to provide pharmaceutical compositions comprising the sulfonamides of formula (I) and methods for their use as inhibitors of HIV aspartyl protease.

30

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description

-11-

is set forth. In the description, the following terms are employed herein:

Unless expressly stated to the contrary, the terms "-SO₂-" and "-S(O)₂-" as used herein refer to a sulfone or sulfone derivative (i.e., both appended groups linked to the S), and not a sulfinic ester.

For the compounds of formula I, and intermediates thereof, the stereochemistry of OR⁷ is defined relative to D on the adjacent carbon atom, when the molecule is drawn in an extended zigzag representation (such as that drawn for compound of formula I). If both OR⁷ and D reside on the same side of the plane defined by the extended backbone of the compound, the stereochemistry of OR⁷ will be referred to as "syn". If OR⁷ and D reside on opposite sides of that plane, the stereochemistry of OR⁷ will be referred to as "anti".

The term "alkyl", alone or in combination with any other term, refers to a straight-chain or branch-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 1 to about 15 and more preferably from 1 to about 10 carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl and the like.

The term "alkenyl," alone or in combination with any other term, refers to a straight-chain or branched-chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 2 to about 18 carbon atoms and more preferably, from 2 to about 8 carbon atoms. Examples of alkenyl radicals include, but

-12-

are not limited to, ethenyl, propenyl, isopropenyl, 1,4-butadienyl, pentenyl and the like.

The term "alkoxy" refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Examples of
5 suitable alkyl ether radicals include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy and the like.

The term "aryl," alone or in combination with any other term, refers to a carbocyclic aromatic radical
10 (such as phenyl or naphthyl) containing the specified number of carbon atoms, preferably from 6-15 carbon atoms, and more preferably from 6-10 carbon atoms, optionally substituted with one or more substituents selected from C1-6 alkoxy, (for example methoxy), nitro,
15 cyano, -SCH₃, halogen, (for example chloro), amino, carboxylate and hydroxy. Examples of aryl radicals include, but are not limited to phenyl, naphthyl, indenyl, indanyl, azulenyl, fluorenyl, anthracenyl and the like.

20 The term "heterocyclyl" or "heterocycle" refers to a stable 3-7 membered monocyclic heterocyclic ring or 8-11 membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which may be optionally benzofused if monocyclic. Each heterocycle consists of
25 one or more carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. As used herein, the terms "nitrogen and sulfur heteroatoms" include any oxidized form of nitrogen and sulfur, and the quaternized form of any basic
30 nitrogen. A heterocyclyl radical may be attached at any endocyclic carbon or heteroatom which results in the creation of a stable structure. Preferred heterocycles include 5-7 membered monocyclic heterocycles and 8-10

-13-

membered bicyclic heterocycles. Examples of such groups include imidazolyl, imidazolinoyl, imidazolidinyl, quinolyl, isoquinolyl, indolyl, indazolyl, indazolinolyl, perhydropyridazyl, pyridazyl, pyridyl, pyrrolyl, 5 pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazinyl, quinoxolyl, piperidinyl, pyranyl, pyrazolinyl, piperazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiamorpholinyl, furyl, thienyl, triazolyl, thiazolyl, carbolinyl, tetrazolyl, thiazolidinyl, benzofuranoyl, 10 thiamorpholinyl sulfone, oxazolyl, benzoxazolyl, oxopiperidinyl, oxopyrrolidinyl, oxoazepinyl, azepinyl, isoxozolyl, isothiazolyl, furazanyl, tetrahydropyranyl, tetrahydrofuranyl, thiazolyl, thiadiazoyl, dioxolyl, dioxinyl, oxathieryl, benzodioxolyl, dithieryl, 15 thiophenyl, tetrahydrothiophenyl, sulfolanyl, dioxanyl, dioxolanyl, tetrahydrofurodihydrofuranyl, tetrahydropyranodihydrofuranyl, dihydropyranyl, tetrahydrofurofuranyl and tetrahydropyranofuranyl.

The term "pharmaceutically effective amount" refers to an amount effective in treating a virus infection, for 20 example an HIV infection, in a patient either as monotherapy or in combination with other agents. The term "treating" as used herein refers to the alleviation of symptoms of a particular disorder in a patient or the improvement of an ascertainable measurement associated 25 with a particular disorder. The term "prophylactically effective amount" refers to an amount effective in preventing a virus infection, for example an HIV infection, in a patient. As used herein, the term 30 "patient" refers to a mammal, including a human.

The terms "HIV protease" and "HIV aspartyl protease" are used interchangeably and refer to the aspartyl protease encoded by the human immunodeficiency virus type

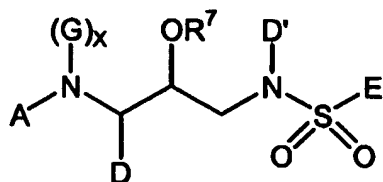
-14-

1 or 2. In a preferred embodiment of this invention, these terms refer to the human immunodeficiency virus type 1 aspartyl protease.

The term "thiocarbamates" refers to compounds
5 containing the functional group N-SO₂-O.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess
10 stability sufficient to allow manufacture and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

15 This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as
20 methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and
25 phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization. The novel sulfonamides of this invention are those of formula I:



(I)

30

-15-

and pharmaceutically acceptable salts thereof;
wherein:

- A is selected from H; Ht; $-R^1\text{-Ht}$; $-R^1\text{-C}_1\text{-C}_6$ alkyl, which is optionally substituted with one or more groups
5 independently selected from hydroxy, $-\text{CN}$, $\text{C}_1\text{-C}_4$ alkoxy, Ht, $-\text{O-Ht}$, $-\text{NR}^2\text{-Ht}$, $-\text{NR}^2\text{-CO-N(R}^2)_2$, $-\text{SO}_2\text{-N(R}^2)_2$, $-\text{SO}_2\text{-R}^2$ or $-\text{CO-N(R}^2)_2$; $-R^1\text{-C}_2\text{-C}_6$ alkenyl, which is optionally substituted with one or more groups independently selected from hydroxy, $\text{C}_1\text{-C}_4$ alkoxy, Ht, $-\text{O-Ht}$,
10 $-\text{NR}^2\text{-CO-N(R}^2)_2$ or $-\text{CO-N(R}^2)_2$; or R^7 ;
each R^1 is independently selected from $-\text{C(O)-}$, $-\text{S(O)}_2\text{-}$, $-\text{C(O)-C(O)-}$, $-\text{O-C(O)-}$, $-\text{O-S(O)}_2\text{-}$, $-\text{NR}^2\text{-}$, $-\text{NR}^2\text{-S(O)}_2\text{-}$, $-\text{NR}^2\text{-C(O)-}$ or $-\text{NR}^2\text{-C(O)-C(O)-}$;
each Ht is independently selected from $\text{C}_3\text{-C}_7$
15 cycloalkyl; $\text{C}_5\text{-C}_7$ cycloalkenyl; $\text{C}_6\text{-C}_{14}$ aryl; or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, $\text{N(R}^2)$, O, S and S(O)_n ; wherein said aryl or said heterocycle is optionally fused to Q; and wherein any member of said Ht is
20 optionally substituted with one or more substituents independently selected from oxo, $-\text{OR}^2$, SR^2 , $-\text{R}^2$, $-\text{N(R}^2)(\text{R}^2)$, $-\text{R}^2\text{-OH}$, $-\text{CN}$, $-\text{CO}_2\text{R}^2$, $-\text{C(O)-N(R}^2)_2$, $-\text{S(O)}_2\text{-N(R}^2)_2$, $-\text{N(R}^2)\text{-C(O)-R}^2$, $-\text{N(R}^2)\text{-C(O)O-R}^2$, $-\text{C(O)-R}^2$, $-\text{S(O)}_n\text{-R}^2$, $-\text{OCF}_3$, $-\text{S(O)}_n\text{-Q}$, methylenedioxy, $-\text{N(R}^2)\text{-S(O)}_2(\text{R}^2)$, halo, $-\text{CF}_3$,
25 $-\text{NO}_2$, Q, $-\text{OQ}$, $-\text{OR}^7$, $-\text{SR}^7$, $-\text{R}^7$, $-\text{N(R}^2)(\text{R}^7)$ or $-\text{N(R}^7)_2$;
each R^2 is independently selected from H, or $\text{C}_1\text{-C}_4$ alkyl optionally substituted with a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially
30 saturated or unsaturated heterocyclic ring containing one or more heteroatoms selected from O, N, S, S(O)_n or $\text{N(R}^{33})$; wherein any of said ring systems or $\text{N(R}^{33})$ is optionally substituted with 1 to 4 substituents

-16-

- independently selected from -X'-Y', -O-arylalkyl, -S-arylalkyl, -N(Y')₂, -N(H)-arylalkyl, -N(C₁-C₄ alkyl)-arylalkyl, oxo, -O-(C₁-C₄ alkyl), OH, C₁-C₄ alkyl, -SO₂H, -SO₂-(C₁-C₄ alkyl), -SO₂-NH₂, -SO₂-NH(C₁-C₄ alkyl),
- 5 -SO₂-N(C₁-C₄ alkyl)₂, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NH-C(O)H, -N(C₁-C₄ alkyl)-C(O)H, -NH-C(O)-C₁-C₄ alkyl, -C₁-C₄ alkyl-OH, -OH, -CN, -C(O)OH, -C(O)O-C₁-C₄ alkyl, -C(O)-NH₂, -C(O)-NH(C₁-C₄ alkyl), -C(O)-N(C₁-C₄ alkyl)₂, halo or -CF₃;
- 10 X' is -O-, -S-, -NH-, -NHC(O)-, -NHC(O)O-, -NHSO₂-, or -N(C₁-C₄)alkyl-;
- Y' is C₁-C₁₅ alkyl, C₂-C₁₅ alkenyl or alkynyl, wherein one to five carbon atoms in Y are optionally substituted with C₃-C₇ cycloalkyl or C₅-C₆ cycloalkenyl, C₆-C₁₄ aryl or
- 15 a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, NH, O, S and S(O)_n;
- each R³ is independently selected from H, Ht, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl or
- 20 C₅-C₆ cycloalkenyl; wherein any member of said R³, except H, is optionally substituted with one or more substituents selected from -OR², -C(O)-N(R²)₂, -S(O)_n-N(R²)₂, -N(R²)₂, -N(R²)-C(O)O(R²), -N(R²)-C(O)N(R²)₂, -N(R²)-C(O)-R², Ht, -CN, -SR², -C(O)OR², N(R²)-C(O)-R²;
- 25 each R³³ is selected from H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl or C₅-C₆ cycloalkenyl, C₆-C₁₄ aryl or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, NH, O, S and S(O)_n;
- 30 each n is independently 1 or 2;
- G, when present, is selected from H, R⁷ or C₁-C₄ alkyl, or, when G is C₁-C₄ alkyl, G and R⁷ are bound to one

-17-

another either directly or through a C₁-C₃ linker to form a heterocyclic ring; or

when G is not present (i.e., when x in (G)_x is 0), then the nitrogen to which G is attached is bound
5 directly to the R⁷ group in -OR⁷ with the concomitant displacement of one -ZM group from R⁷;

D is selected from C₁-C₆ alkyl which is substituted with Q, which is optionally substituted with one or more groups selected from C₃-C₆ cycloalkyl, -R³, -O-Q or Q;
10 C₂-C₄ alkenyl which is substituted with Q, which is optionally substituted with one or more groups selected from -OR², -S-Ht, -R³, -O-Q or Q; C₃-C₆ cycloalkyl, which is optionally substituted with or fused to Q; or C₅-C₆ cycloalkenyl, which is optionally substituted with or
15 fused to Q;

each Q is independently selected from a 3-7 membered saturated, partially saturated or unsaturated carbocyclic ring system; or a 5-7 membered saturated, partially saturated or unsaturated heterocyclic ring containing one
20 or more heteroatoms selected from O, N, S, S(O)_n or N(R²); wherein Q contains one substituent selected from -OR², -OR⁸, -O-arylalkyl, -SR⁸, -S-arylalkyl, -N(R²)R⁸, -N(R²)-arylalkyl and may be optionally substituted with one or more additional substituents independently selected
25 from oxo, -OR⁸, -O-arylalkyl -SR⁸, -S-arylalkyl, -N(R²)R⁸, -N(R²)-arylalkyl, -OR², -R², -SO₂R², -SO₂-N(R²)₂, -N(R²)₂, -N(R²)-C(O)-R², -OH, (C₁-C₄)-OH, -CN, -CO₂R², -C(O)-N(R²)₂, halo or -CF₃;

each R⁸ is independently selected from Ht, -C₁-C₁₅
30 branched or straight chain alkyl, alkenyl or alkynyl wherein one to five carbon atoms in said alkyl, alkenyl or alkynyl are independently replaced by W, or wherein one to five carbon atoms in said alkyl, alkenyl or

-18-

alkynyl are substituted with Ht; and wherein R⁸ is additionally and optionally substituted with one or more groups independently selected from -OH, -S(C₁-C₆ alkyl), -CN, -CF₃, -N(R²)₂, halo, -C₁-C₄-alkyl, -C₁-C₄-alkoxy; -Ht; -O-Ht; -NR²-CO-N(R²)₂; -CO-N(R²)₂; -R¹-C₂-C₆ alkenyl, which is optionally substituted with one or more groups independently selected from hydroxy, C₁-C₄ alkoxy, Ht, -O-Ht, -NR²-CO-N(R²)₂ or -CO-N(R²)₂; or R⁷;

wherein W is -O-, -NR²-, -S-, -C(O)-, -C(S)-, -C(=NR²)-, -S(O)₂-, -NR²-S(O)₂-, -S(O)₂-NR²-, -NR²-C(O)O-, -O-C(O)NR²-, -NR²-C(O)NR²-, -NR²-C(S)NR²-, -CONR², -NR²C(O)-, -C(S)NR², -NR²C(S)-, -NR²-C(=N-CN)-NR²-, -NR²C(=N-CN)O- or -C(O)O-;

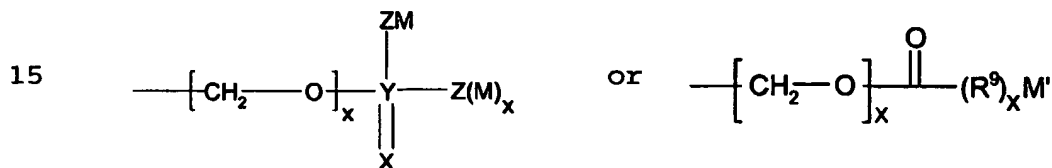
D' is selected from C₁-C₁₅ alkyl, C₁-C₁₅ alkoxy, C₂-C₁₅ alkenyl, C₂-C₁₅ alkenyloxy, C₂-C₁₅ alkynyl, or C₂-C₁₅ alkynyloxy, wherein D' optionally comprises one or more substituents independently selected from Ht, oxo, halo, -CF₃, -OCF₃, -NO₂, azido, -SH, -SR³, -N(R³)-N(R³)₂, -O-N(R³)₂, -(R³)N-O-(R³), -N(R³)₂, -CN, -CO₂R³, -C(O)-N(R³)₂, -S(O)_n-N(R³)₂, -N(R³)-C(O)-R³, -N(R³)-C(O)-N(R³)₂, -C(O)-R³, -S(O)_n-R³, -N(R³)-S(O)_n(R³), -N(R³)-S(O)_n-N(R³)₂, -S-NR³-C(O)R³, -C(S)N(R³)₂, -C(S)R³, -NR³-C(O)OR³, -O-C(O)OR³, -O-C(O)N(R³)₂, -NR³-C(S)R³, =N-OH, =N-OR³, =N-N(R³)₂, =NR³, =NNR³C(O)N(R³)₂, =NNR³C(O)OR³, =NNR³S(O)_n-N(R³)₂, -NR³-C(S)OR³, -NR³-C(S)N(R³)₂, -NR³-C[=N(R³)]-N(R³)₂, -N(R³)-C[=N-NO₂]-N(R³)₂, -N(R³)-C[=N-NO₂]-OR³, -OC(O)R³, -OC(S)R³, -OC(O)N(R³)₂, -C(O)N(R³)-N(R³)₂, -N(R³)-N(R³)C(O)R³, -N(R³)-OC(O)R³, -N(R³)-OC(O)R³, -N(R³)-OC(S)N(R³)₂, -OC(S)N(R³)(R³), or -PO₃-R³;

E is selected from Ht; O-Ht; Ht-Ht; Ht fused with Ht; -O-R³; -N(R²)(R³); -N(R²)-Ht; C₁-C₆ alkyl, which is optionally substituted with one or more groups selected

from R^4 or Ht; C_2-C_6 alkenyl, which is optionally substituted with one or more groups selected from R^4 or Ht; C_3-C_6 saturated carbocycle, which is optionally substituted with one or more groups selected from R^4 or Ht; or C_5-C_6 unsaturated carbocycle, which is optionally substituted with one or more groups selected from R^4 or Ht;

each R^4 is independently selected from $-R^2$, $-OR^2$, $-OR^3$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-CO_2R^2$, $-OC(O)-R^2$, $-C(O)-N(R^2)_2$, $-C(O)-NR^2(OR^2)$, $-S(O)_2-N(R^2)_2$, halo, $-NR^2-C(O)-R^2$, $-NR^2-OR^2$, $-N(R^2)_2$ or $-CN$;

each R^7 is independently selected from hydrogen,



wherein each M is independently selected from H, Li, Na, K, Mg, Ca, Ba, $-N(R^2)_4$, C_1-C_{12} -alkyl, C_2-C_{12} -alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group, other than the $-CH_2$ that is bound to Z, is optionally replaced by a heteroatom group selected from O, S, $S(O)$, $S(O)_2$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-C_1-C_4$ alkyl, $-N(R^2)_2$, $-N(R^2)_3$, $-OH$, $-O-(C_1-C_4 \text{ alkyl})$, $-CN$, $-C(O)OR^2$, $-C(O)-N(R^2)_2$, $S(O)_2-N(R^2)_2$, $-N(R^2)-C(O)-R_2$, $C(O)R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-R^6$, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

M' is H, C_1-C_{12} -alkyl, C_2-C_{12} -alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from

-20-

O, S, S(O), S(O)₂, or N(R²); and wherein any hydrogen in said alkyl, alkenyl or R⁶ is optionally replaced with a substituent selected from oxo, -OR², -C₁-C₄ alkyl, -N(R²)₂, N(R²)₃, -OH, -O-(C₁-C₄ alkyl), -CN, -C(O)OR², -C(O)-N(R²)₂,
 5 -S(O)₂-N(R²)₂, -N(R²)-C(O)-R₂, -C(O)R², -S(O)_n-R², -OCF₃,
 -S(O)_n-R⁶, -N(R²)-S(O)₂(R²), halo, -CF₃, or -NO₂;

x is 0 or 1;

Z is O, S, N(R²)₂, or, when M is not present, H.

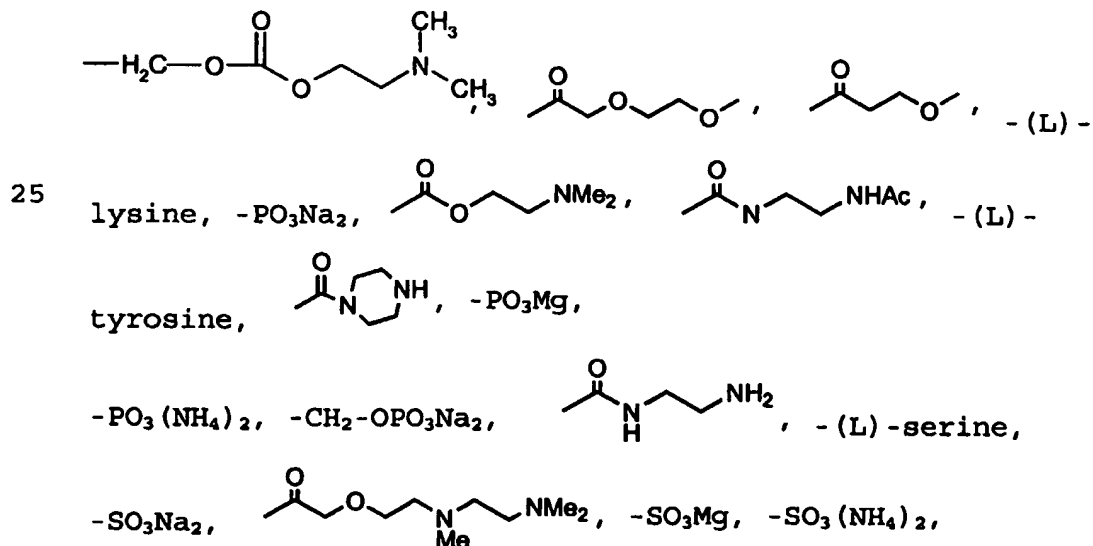
Y is P or S;

10 X is O or S; and

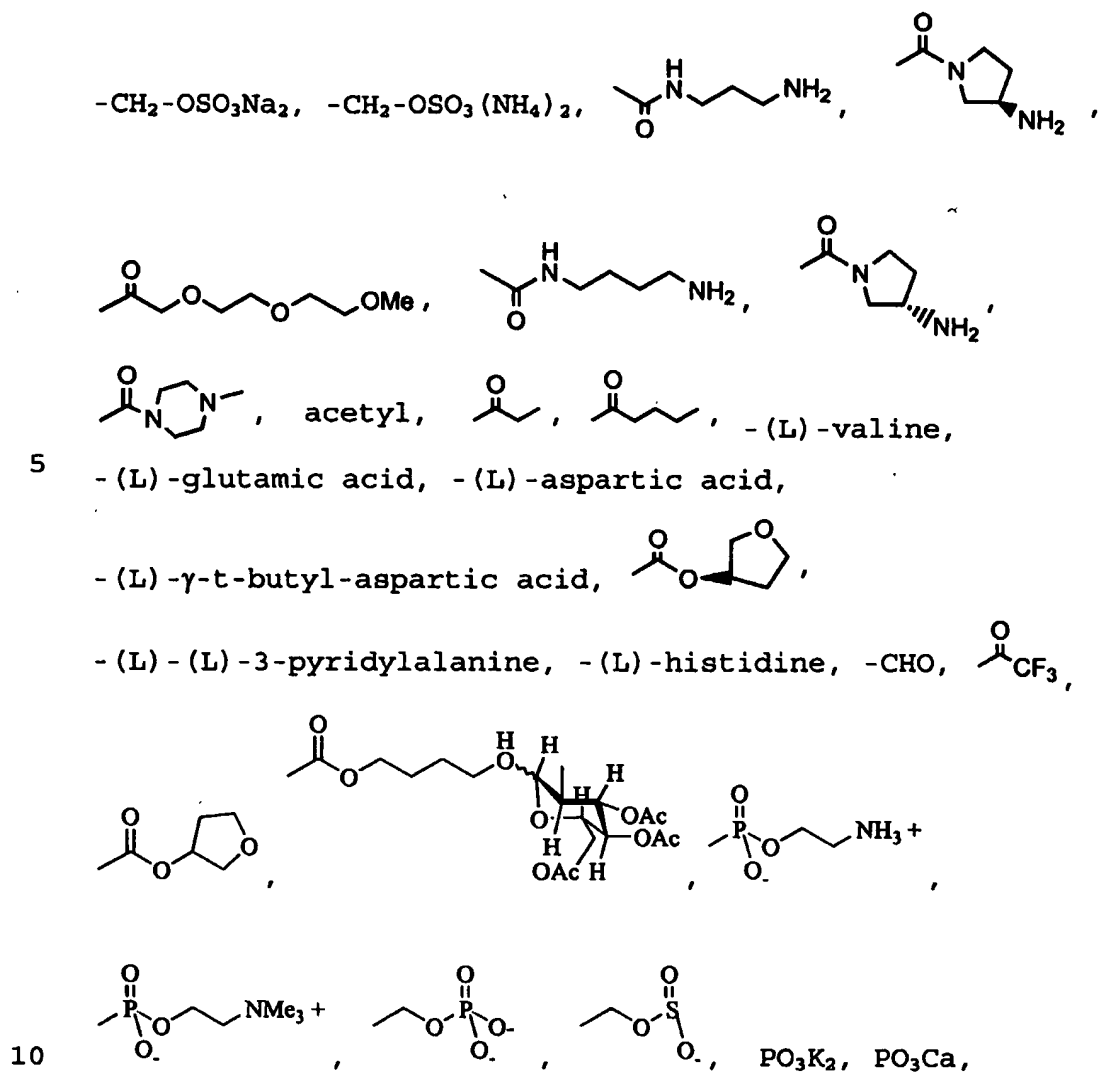
R⁹ is C(R²)₂, O or N(R²); and wherein when Y is S, Z is not S; and

R⁶ is a 5-6 membered saturated, partially saturated or unsaturated carbocyclic or heterocyclic ring system,
 15 or an 8-10 membered saturated, partially saturated or unsaturated bicyclic ring system; wherein any of said heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, S(O)_n or N(R²); and wherein any of said ring systems optionally contains 1 to
 20 4 substituents independently selected from -OH, -C₁-C₄ alkyl, -O-(C₁-C₄ alkyl) or -O-C(O)-(C₁-C₄ alkyl).

Preferably, at least one R⁷ is selected from:



-21-



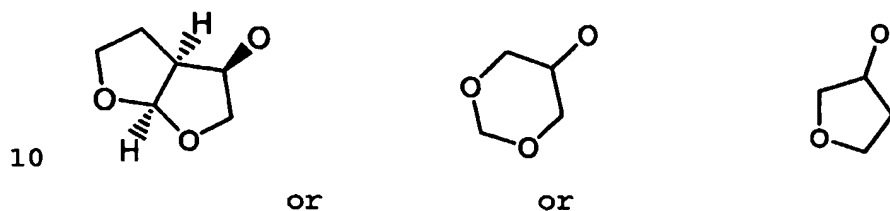
PO_3 -spermine, PO_3 -(spermidine) $_2$ or PO_3 -(meglamine) $_2$.

It will be understood by those of skill in the art that component M or M' in the formulae set forth herein will have either a covalent, a covalent/ zwitterionic, or an ionic association with either Z or R⁹ depending upon the actual choice for M or M'. When M or M' is hydrogen, alkyl, alkenyl, or R⁶, M or M' is covalently bound to R⁹ or Z. If M is a mono- or bivalent metal or other charged species (i.e., NH₄⁺), there is an ionic interaction between M and Z and the resulting compound is a salt.

-22-

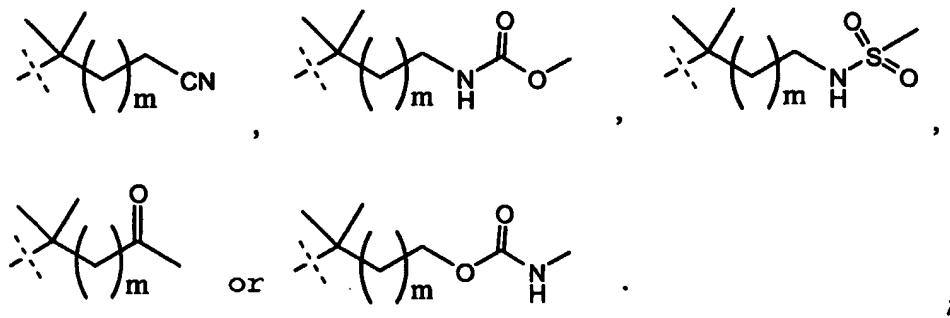
When x is 0 in $(M)_x$, Z may be a charged species. When that occurs, the other M may be oppositely charged to produce a 0 net charge on the molecule. Alternatively, the counter ion may be located elsewhere in the molecule.

According to yet another preferred embodiment, A is $R'-C(O)$, wherein R' is selected from any of the R' groups indicated in Tables 1, 2 and 3, below. More preferably, R' is selected from $-R^1-C_1-C_6$ alkyl,



In another preferred embodiment, D' is $-CH_2-R''$, wherein R'' is selected from any of the R'' groups indicated in Tables 1, 2 and 3, below. More preferably,

15 R'' is selected from:

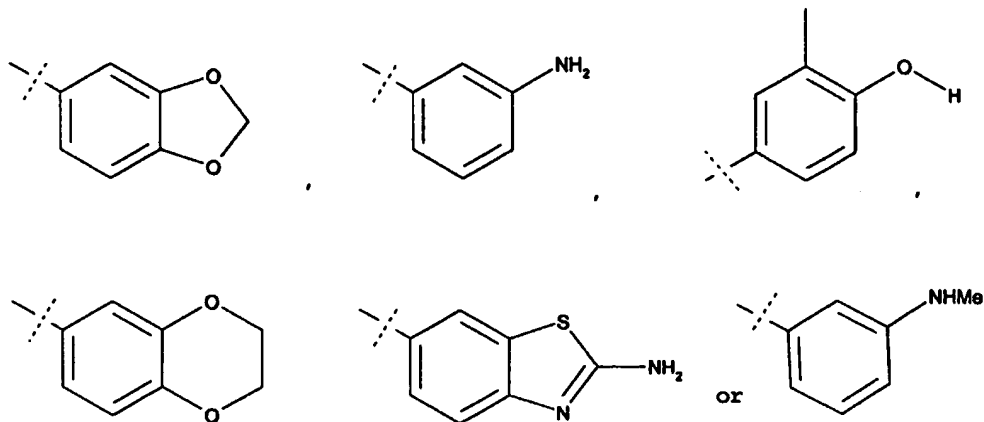


wherein m is 0 to 3.

According to another preferred embodiment, E is selected from any of the E groups indicated in Tables 1,

-23-

2 and 3, below. More preferably, E is selected from:



Preferably, W is -O-, -NR²-, -NR²-S(O)₂-, -NR²-C(O)O-,
 -O-C(O)NR²-, -NR²-C(O)NR²-, -NR²-C(S)NR²-, -NR²C(O)-,
 5 -C(O)NR², -NR²-C(=N-CN)-NR²-, -NR²C(=N-CN)O- or -C(O)O-.

More preferably, W is -NR²-, -NR²C(O)- or -C(O)NR².
 Most preferably, W is -NH-, -NHC(O) or -C(O)NH-.

According to a preferred embodiment, R⁸ is -C₁-C₄-
 branched or straight chain alkyl, wherein one to two
 10 carbon atoms in said alkyl are independently replaced by
 W, wherein R⁸ is additionally and optionally substituted
 with one or more groups independently selected from -OH;
 -C₁-C₄-alkoxy; -Ht; -O-Ht; -NR²-CO-N(R²)₂; -CO-N(R²)₂;
 -R¹-C₂-C₆ alkenyl, which is optionally substituted with
 15 one or more groups independently selected from hydroxy,
 C₁-C₄ alkoxy, Ht, -O-Ht, -NR²-CO-N(R²)₂; -CO-N(R²)₂; or R⁷.

According to another preferred embodiment, R⁸ is Ht,
 wherein Ht is C₆₋₁₄ aryl or a 5-7 membered saturated or
 unsaturated heterocycle, containing one or more
 20 heteroatoms selected from N, N(R²), O, S and S(O)_n,
 wherein Ht is optionally substituted as defined above.

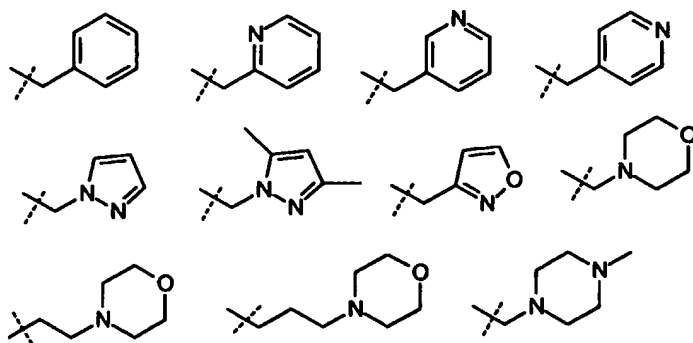
According to another preferred embodiment, R⁸ is a
 -C₁-C₄-branched or straight alkyl chain, wherein one to
 two carbon atoms are substituted with Ht, wherein Ht is
 25 C₆₋₁₄ aryl or a 5-7 membered saturated or unsaturated

-24-

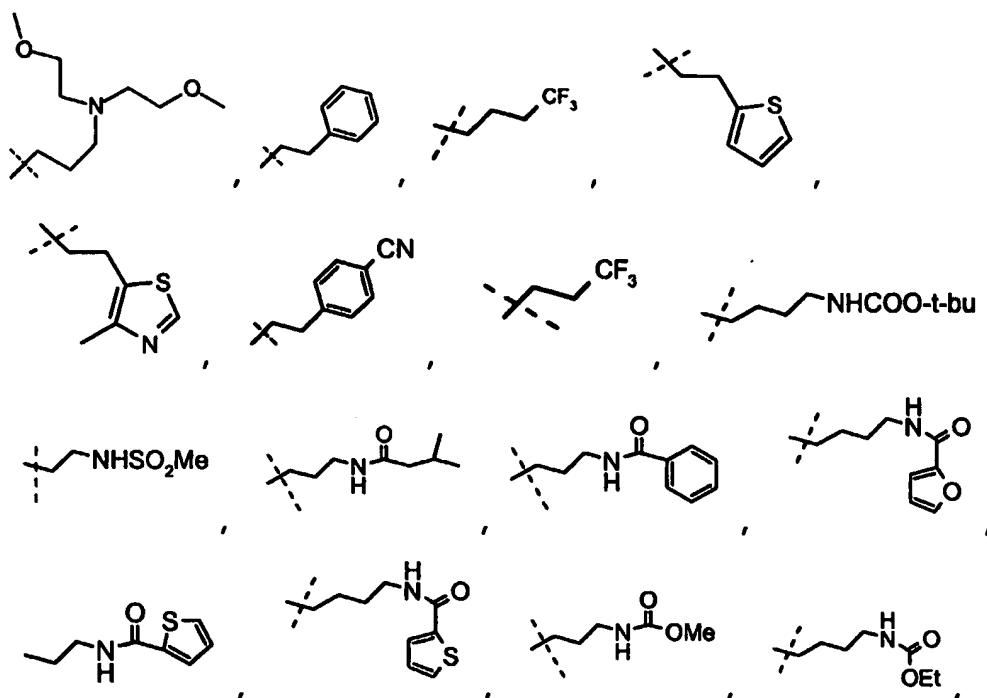
heterocycle, containing one or more heteroatoms selected from N, N(R²), O, S and S(O)_n, wherein Ht is optionally substituted as defined above.

According to a more preferred embodiment, R⁸ is a
5 -C₁-C₄-branched or straight alkyl chain, wherein one carbon atom in said alkyl chain is substituted with Ht, wherein Ht is phenyl or Ht is a 5-6 membered saturated or unsaturated heterocycle, containing one or more
10 heteroatoms selected from N, N(R²), O and S, wherein Ht is optionally substituted as defined above. Preferably, said Ht in R⁸ is selected from 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, thiazolyl, morpholinyl, pyrimidinyl, thiazolidinyl, imidazolyl, 1,2,3-triazolyl, pyrrolidinyl, pyrazolyl,
15 piperazyl, 1,2,4-oxadiazolyl, 4-4'-thiadiazolyl, 1,2,3-thiadiazolyl, isoxazolyl, and isothiazolyl, wherein said Ht is optionally substituted, as defined above. More preferably, R⁸ is selected from any of the R⁸ groups depicted in Tables 1, 2 and 3.

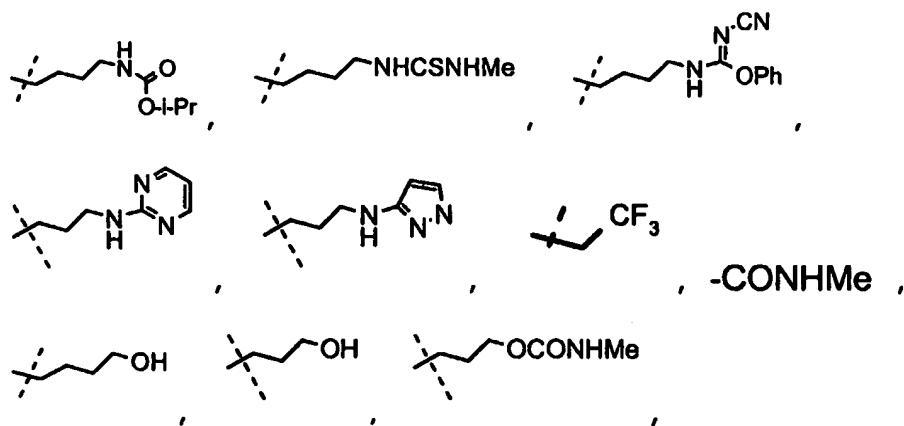
20 Most preferably, R⁸ is selected from:



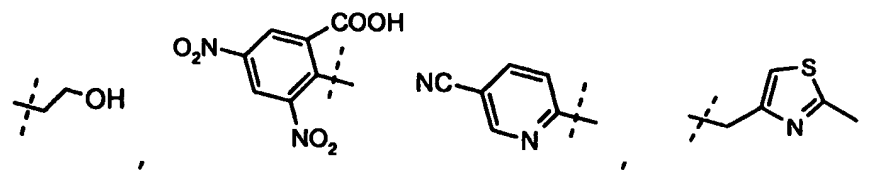
-25-



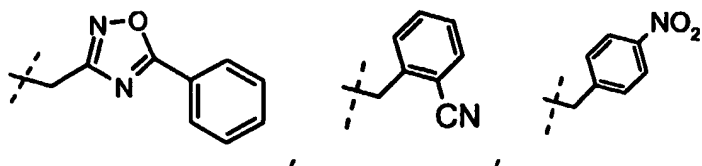
5



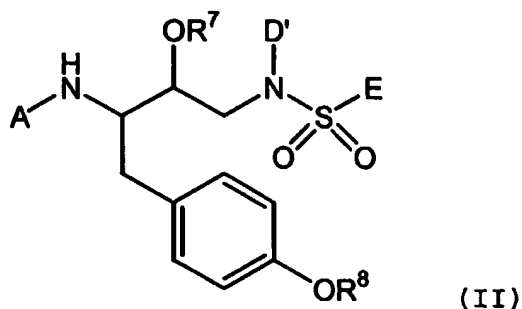
10



-26-



More preferred compounds of formula I are those represented by formula II:



5

wherein A, R⁷, D', E and R⁸ are as defined above.

Preferred compounds of formula II set forth above are those, wherein R⁷ in -OR⁷ is -PO(OM)₂ or
 10 C(O)CH₂OCH₂CH₂OCH₂CH₂OCH₃; wherein M is H, Li, Na, Ca, Mg, K or C₁-C₄ alkyl.

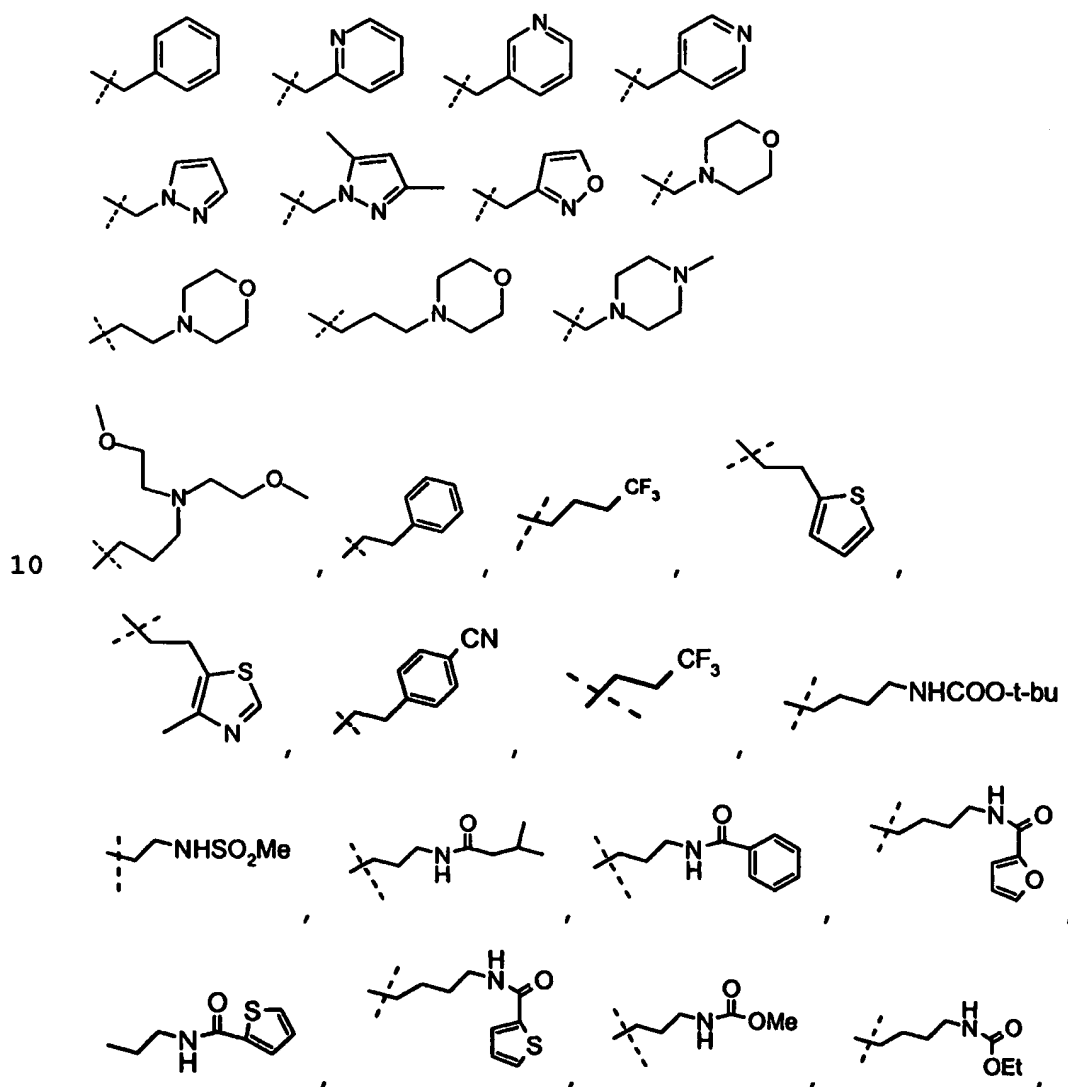
Also preferred are compounds of formula II, wherein R⁸ is selected from -C₁-C₁₅ branched or straight chain alkyl, alkenyl or alkynyl wherein one to five carbon
 15 atoms in said alkyl, alkenyl or alkynyl are independently replaced by W, or wherein one to five carbon atoms in said alkyl, alkenyl or alkynyl are substituted with Ht; and wherein R⁸ is additionally and optionally substituted with one or more groups independently selected from -OH,
 20 -SCH₃, -CN, -CF₃, amino, halo, -C₁-C₄-alkyl, -C₁-C₄-alkoxy; -Ht; -O-Ht; -NR²-CO-N(R²)₂; -CO-N(R²)₂; -R¹-C₂-C₆ alkenyl, which is optionally substituted with one or more groups

-27-

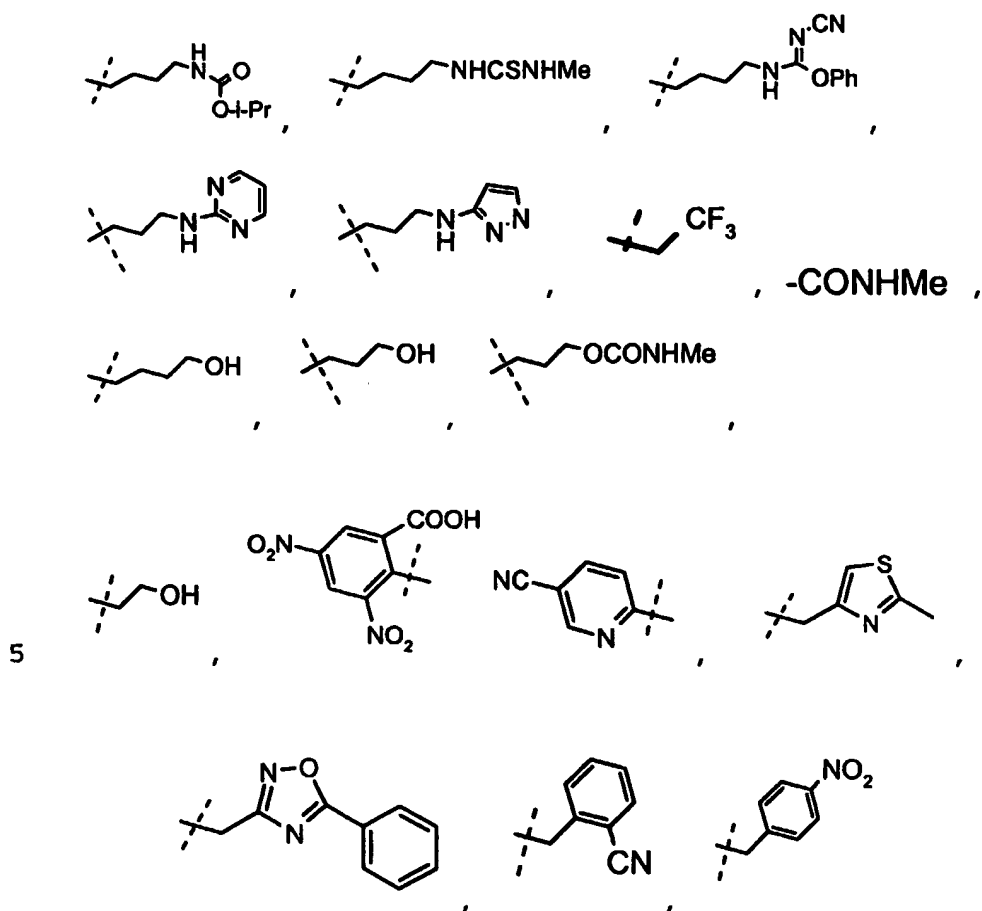
independently selected from hydroxy, C_1 - C_4 alkoxy, Ht, $-O$ -Ht, $-NR^2-CO-N(R^2)_2$ or $-CO-N(R^2)_2$; or R^7 .

More preferably, R^8 in compounds of formula II is selected from any of the R^8 groups depicted in Tables 1, 2 and 3. According to another more preferred embodiment, R^8 in compounds of formula II is selected from the group consisting of:

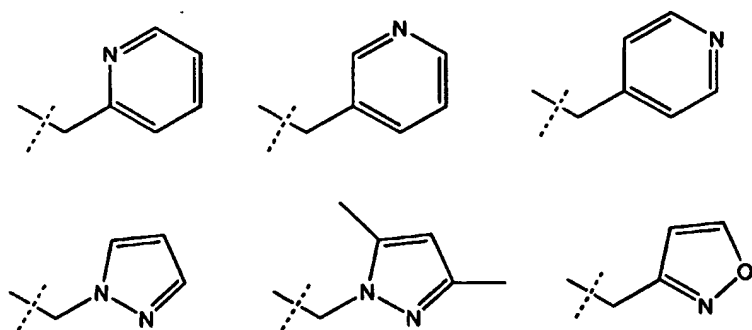
Most preferably, R^8 is selected from:

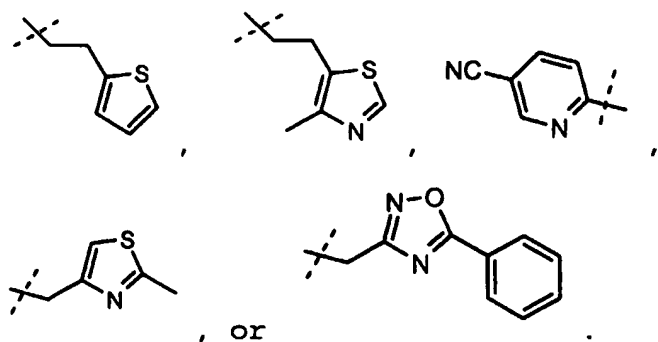


-28-

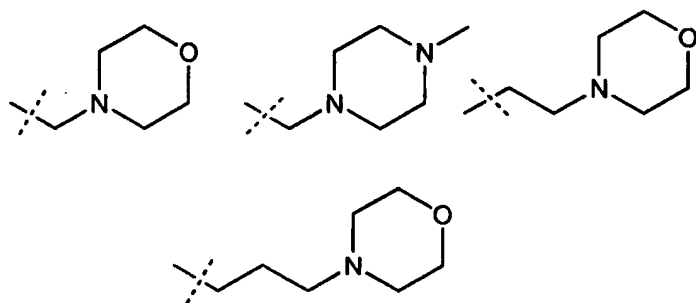


According to another more preferred embodiment, R⁸ is
 10 selected from:

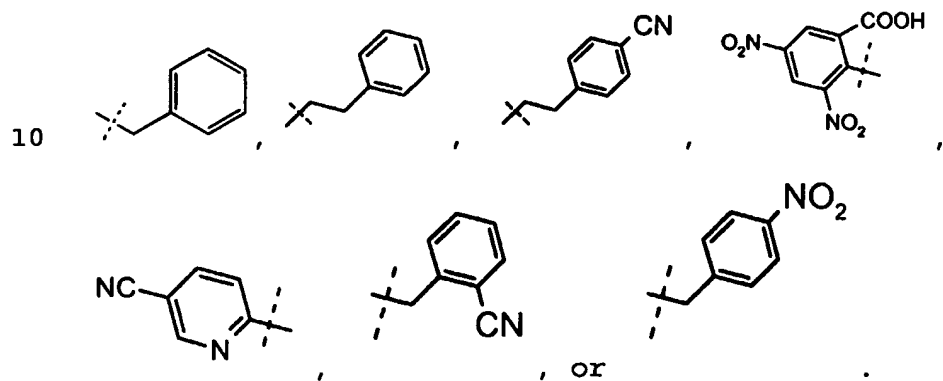




According to another more preferred embodiment, R^8 is
5 selected from:

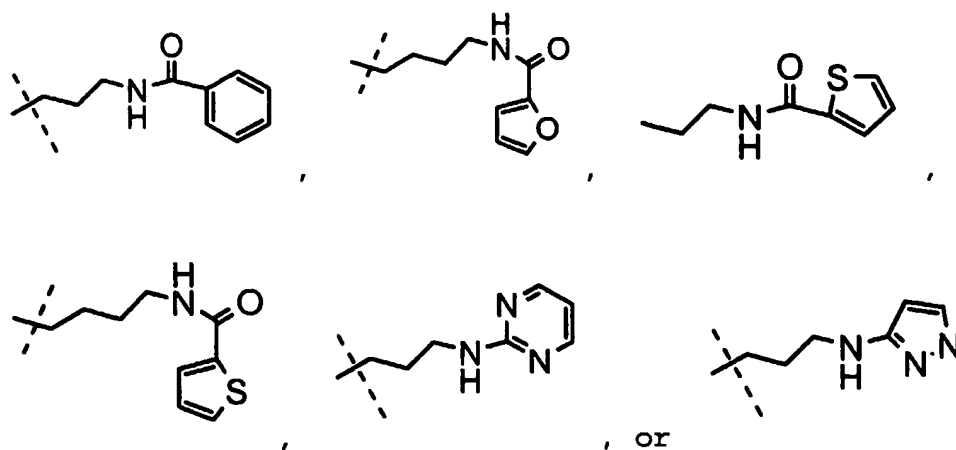


According to another more preferred embodiment, R^8 is selected from:

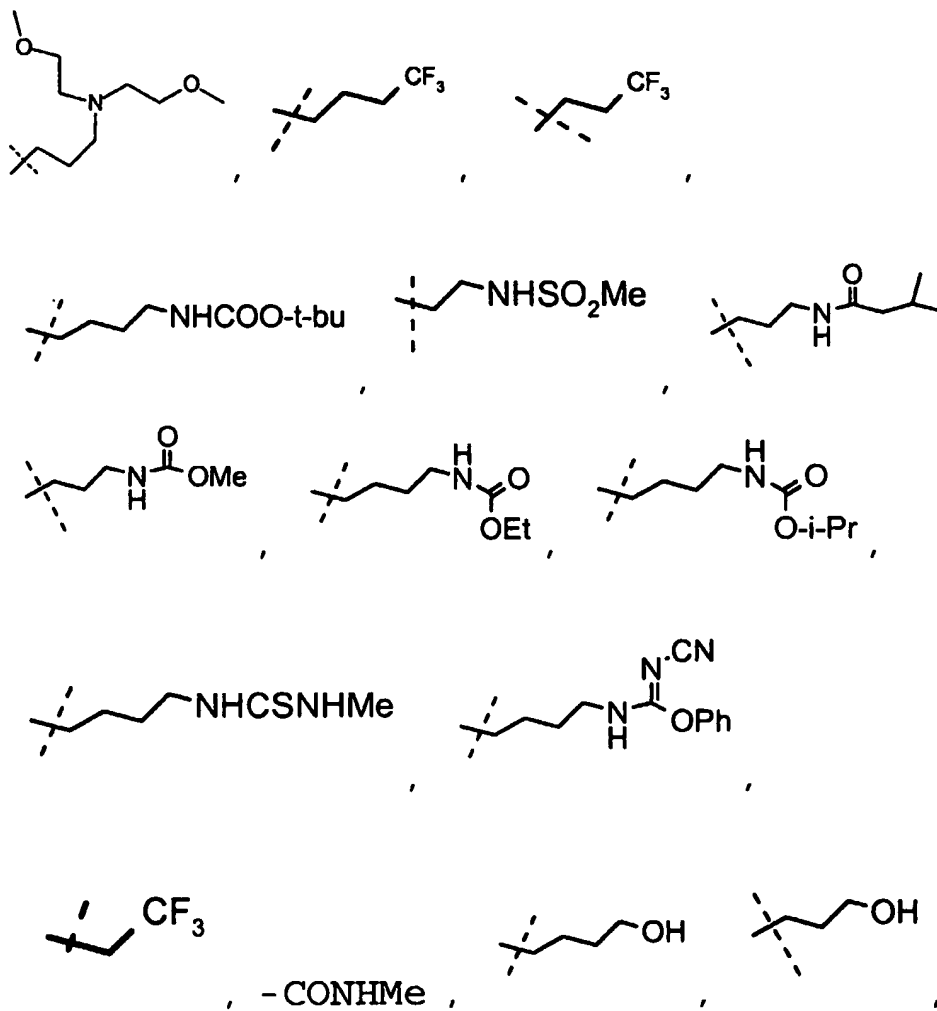


According to another more preferred embodiment, R^8 is selected from:

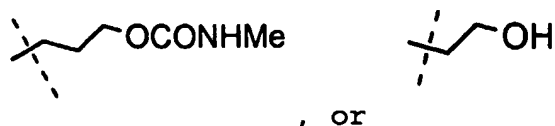
-30-



According to another more preferred embodiment, R⁸ is
 5 selected from:



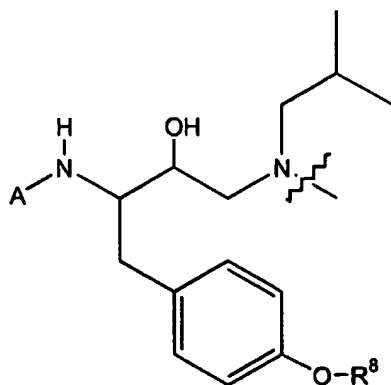
-31-

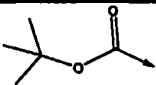
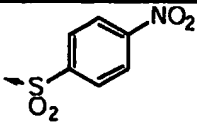
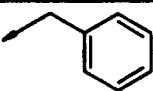
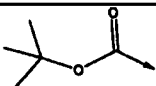
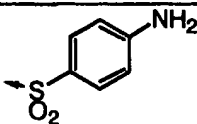
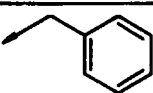
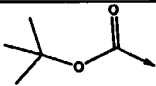
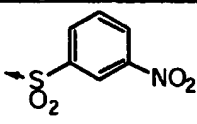
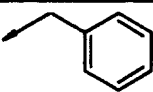
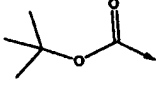
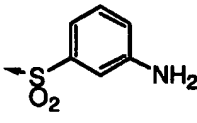
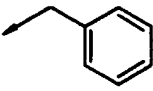
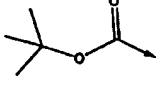
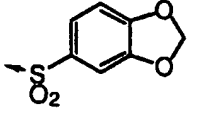
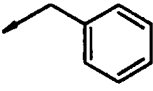
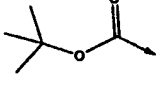
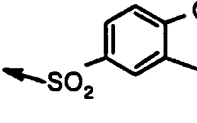
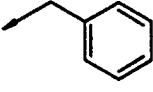
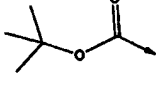
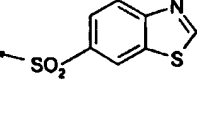
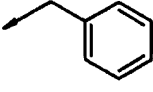
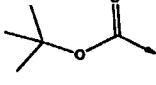
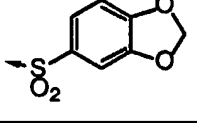
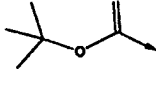
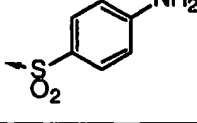
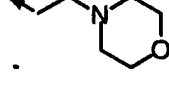
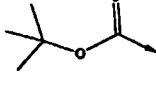
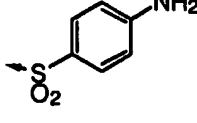
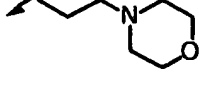
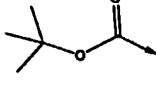
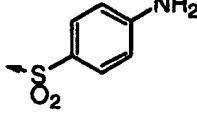
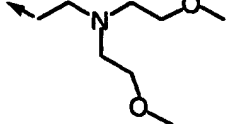


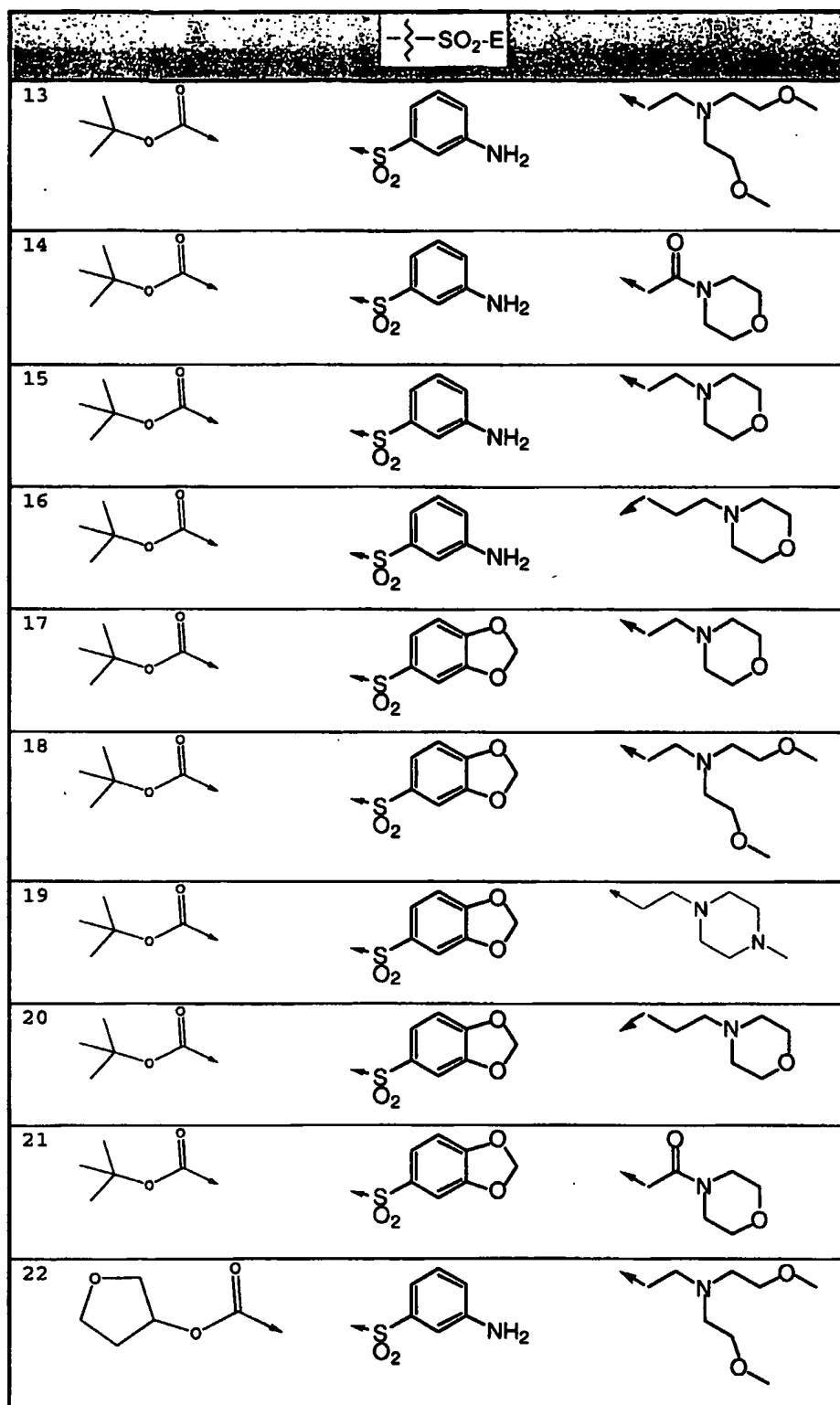
The compounds according to the invention contain one or more asymmetric carbon atoms and thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although the specific compounds exemplified in this application may be depicted in a particular stereochemical configuration, compounds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

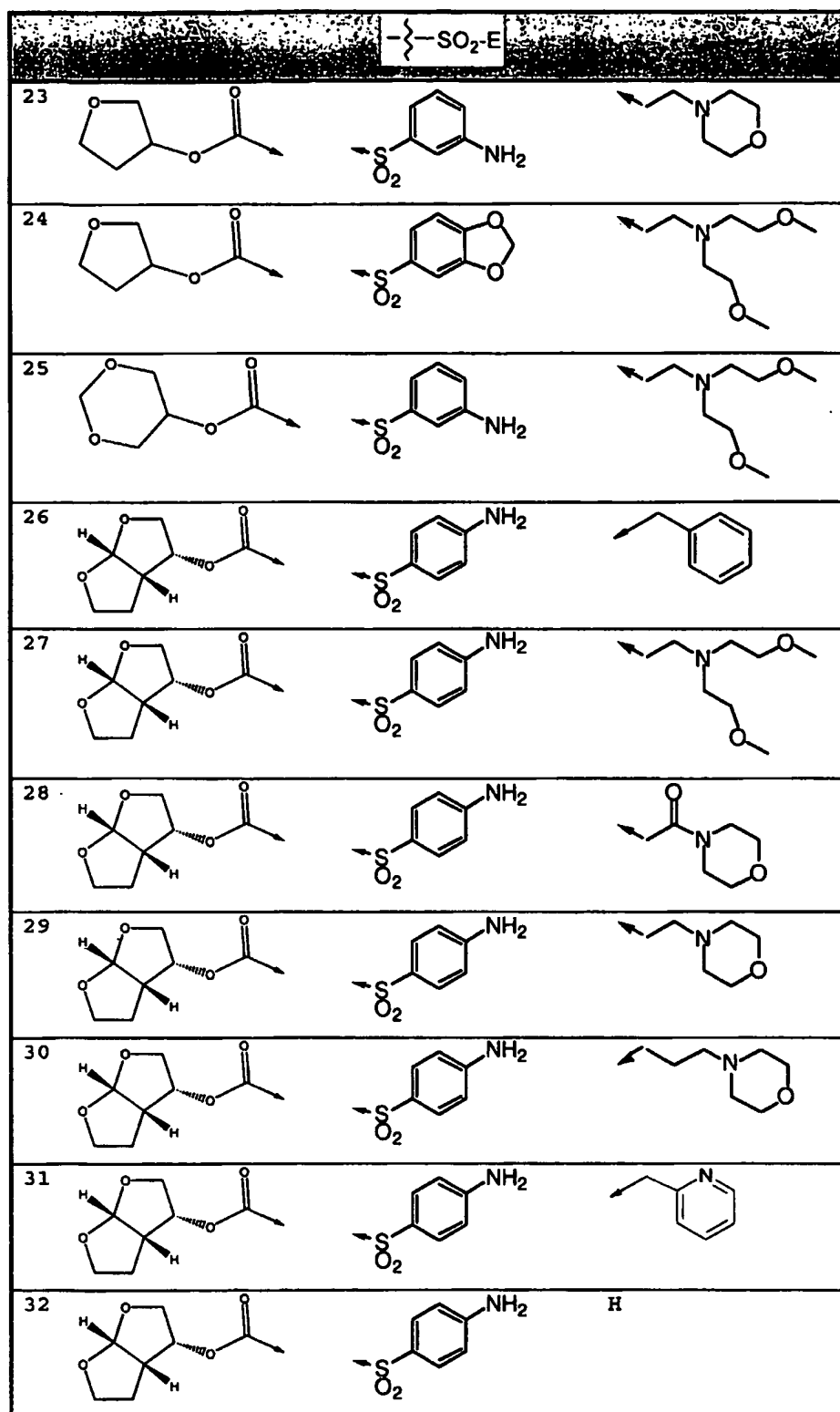
Specific preferred compounds of the present invention are set forth below in Tables 1, 2 and 3. The arrows in Tables 1 and 2, and the dotted lines in Table 3 indicate where the indicated moiety attaches to the rest of the molecule.

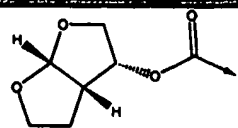
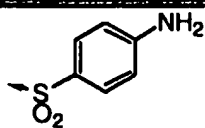
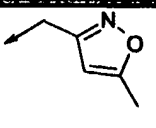
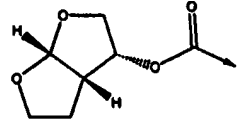
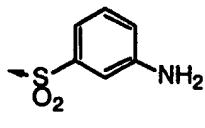
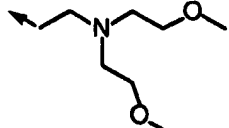
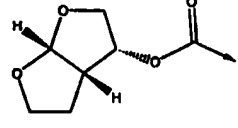
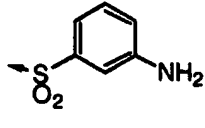
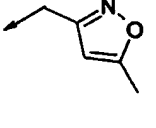
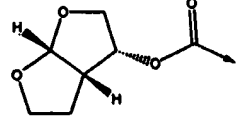
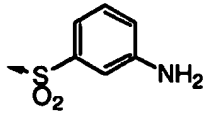
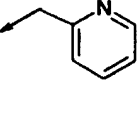
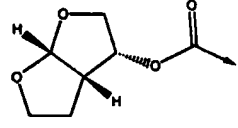
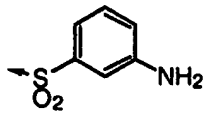
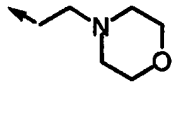
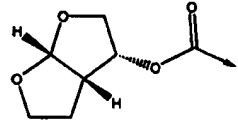
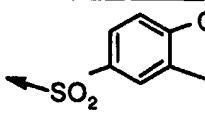
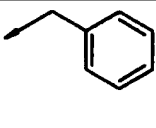
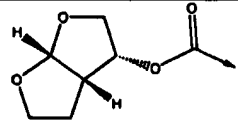
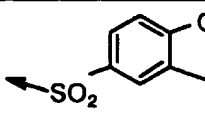
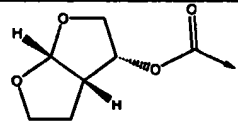
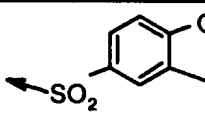
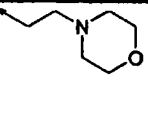
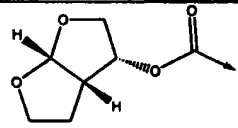
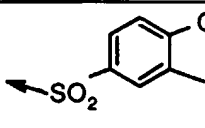
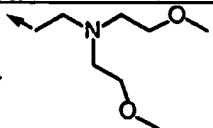
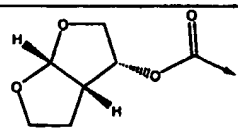
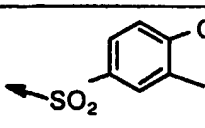
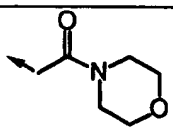
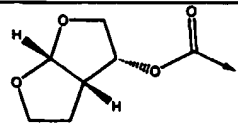
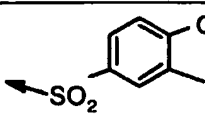
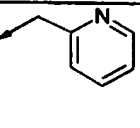
Table 1:

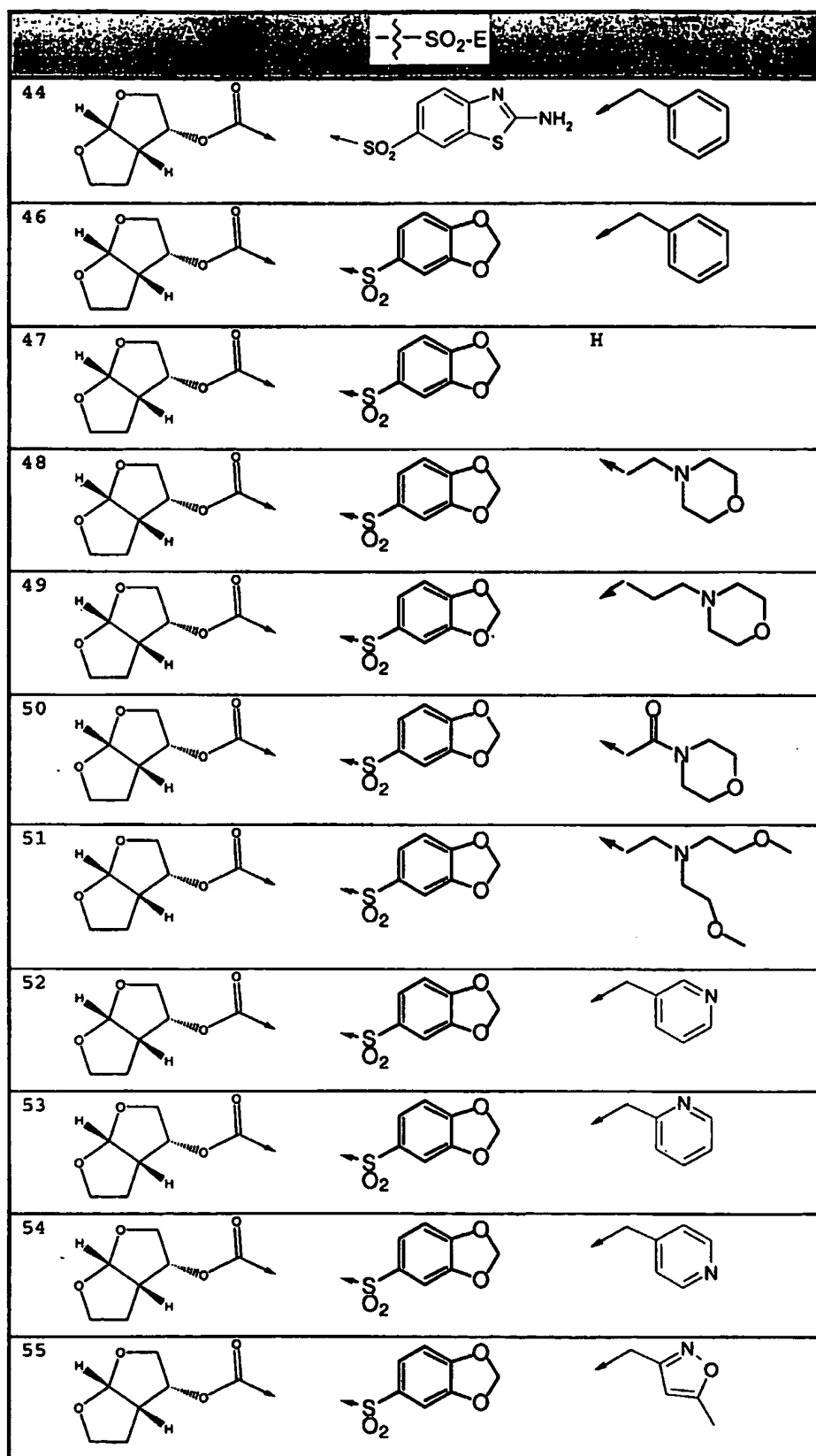


	A	$-\text{SO}_2\text{-E}$	R^5
5a			
5b			
5c			
5d			
5e			
5f			
5g			
6e			H
10			
11			
12			





	A	$-\text{SO}_2\text{E}-$	R^0
33			
34			
35			
36			
37			
38			
39			H
40			
41			
42			
43			



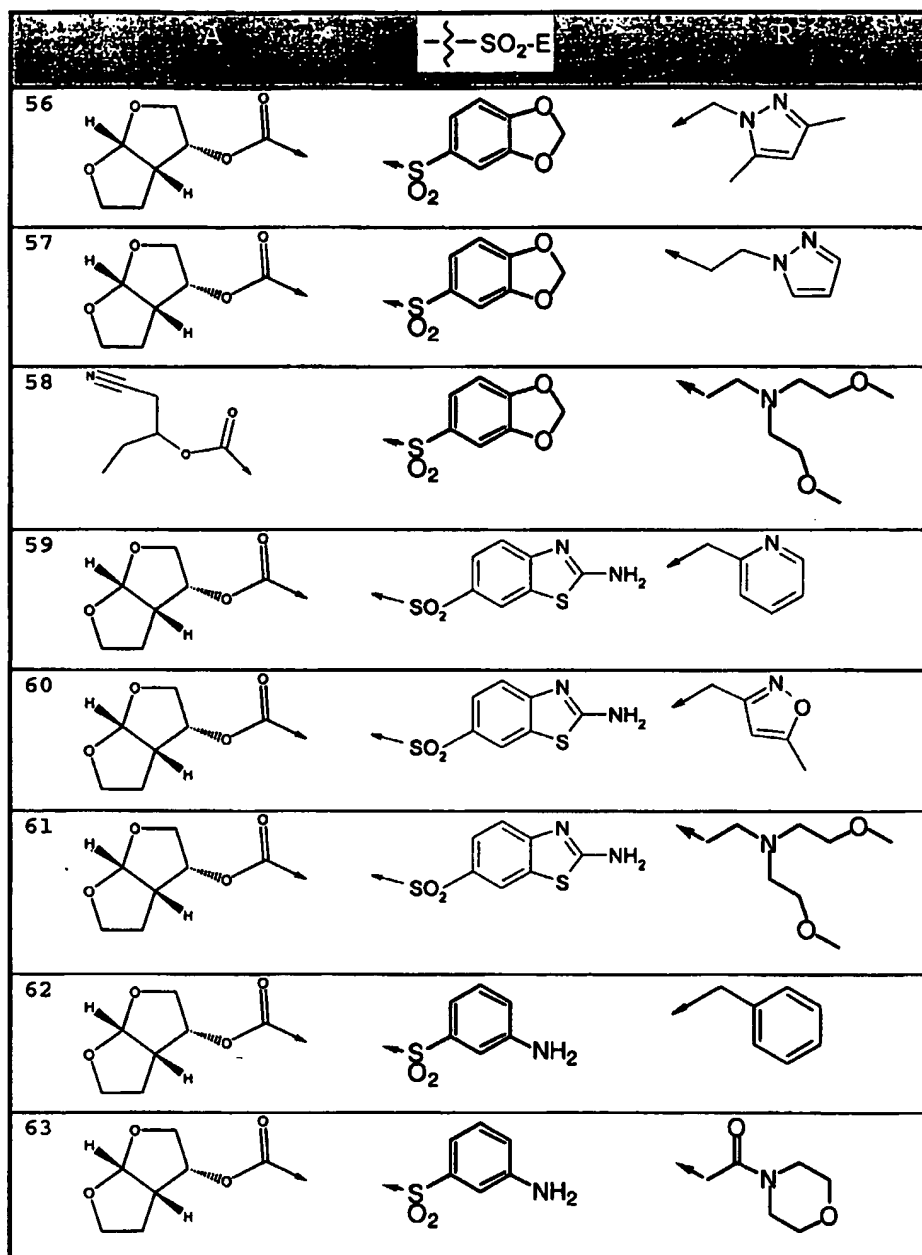
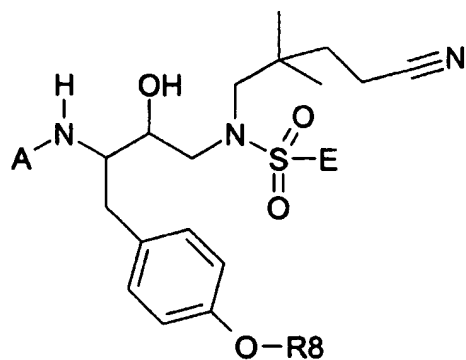
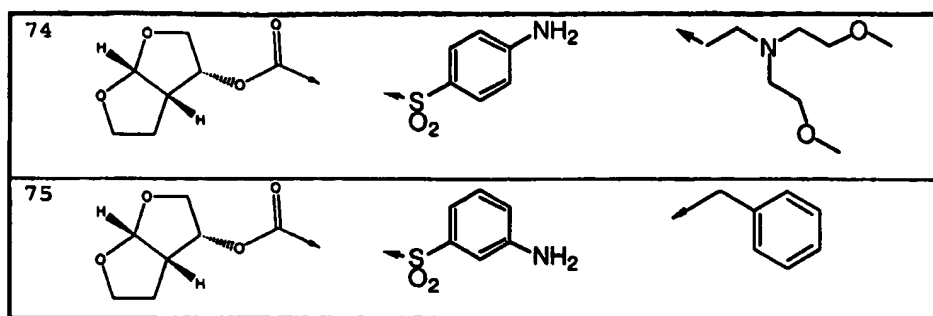
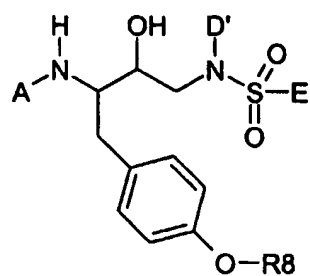
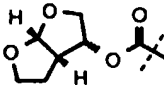

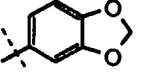
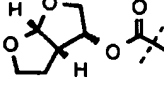
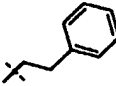

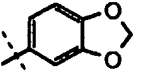
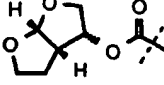
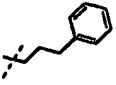

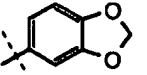
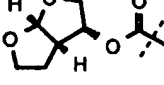
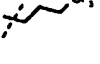

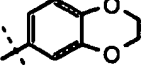


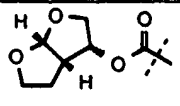
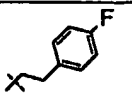
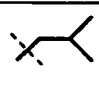
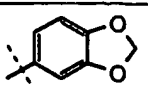
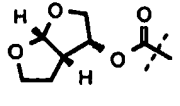
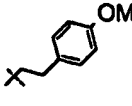
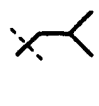
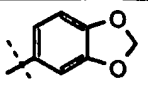
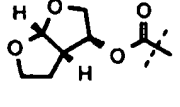
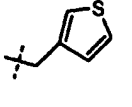
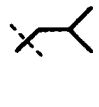
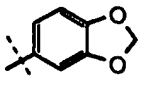
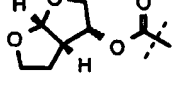
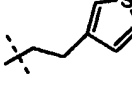
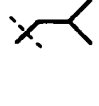
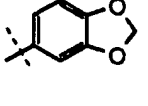
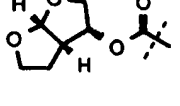
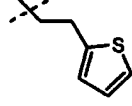
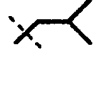
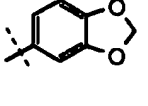
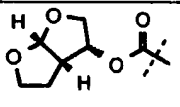
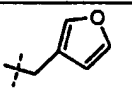
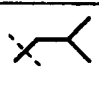
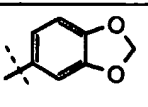
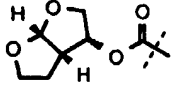
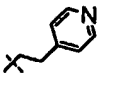
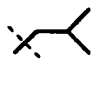
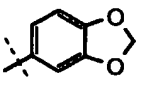
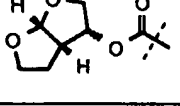
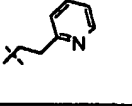
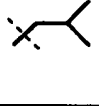
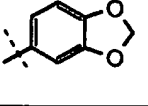
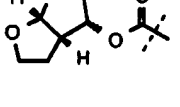
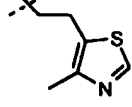
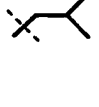
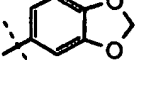
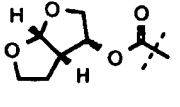
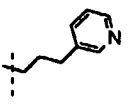
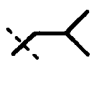
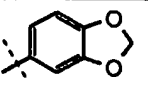
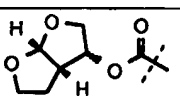
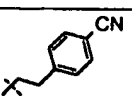
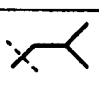
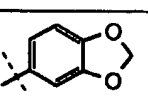
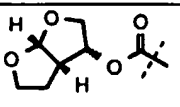
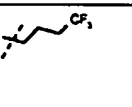
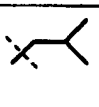
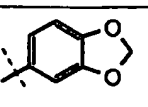
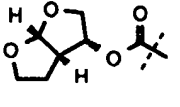
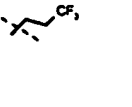
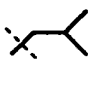
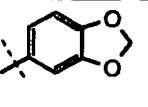
Table 2:

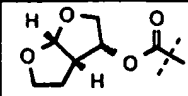
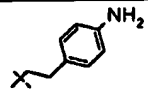

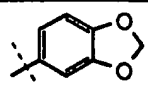
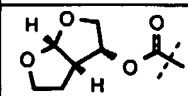
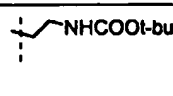

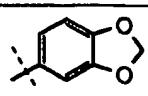
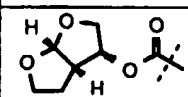
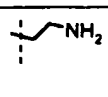

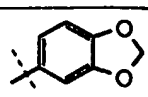
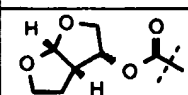
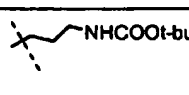

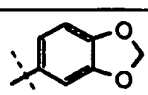
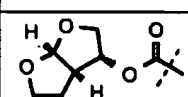
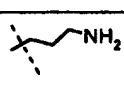

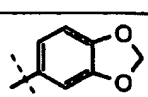
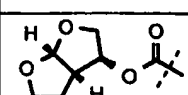
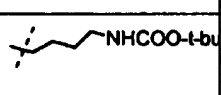

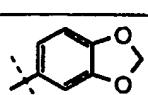
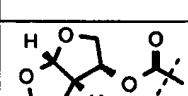
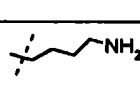

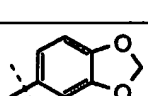
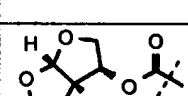
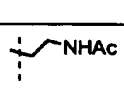

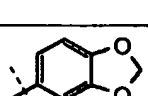
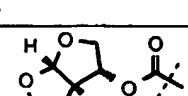
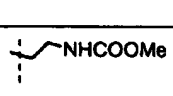

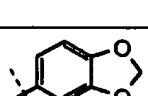
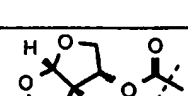
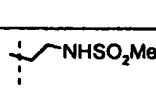

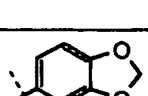
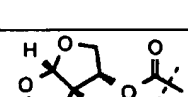


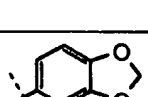
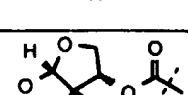
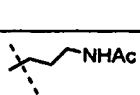

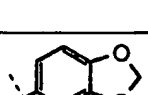
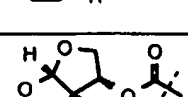
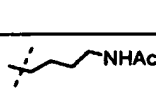


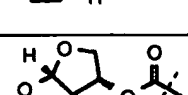
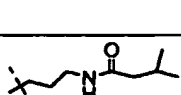

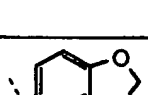


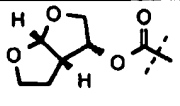
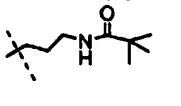
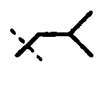
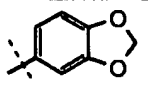
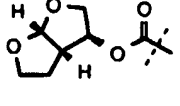
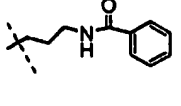
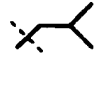
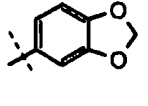
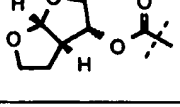
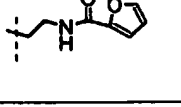
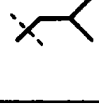
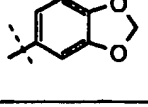
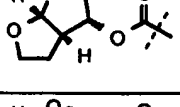
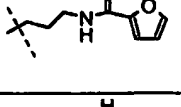

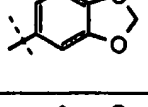
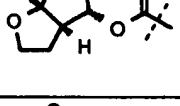
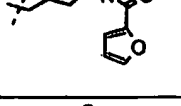

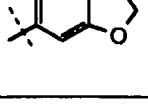
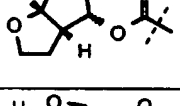
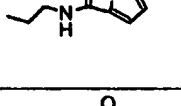

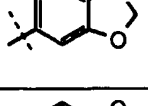
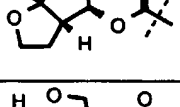
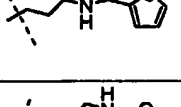
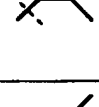
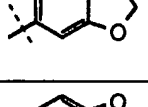
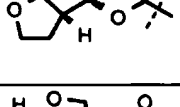
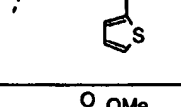
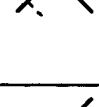
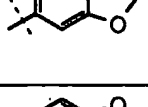
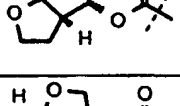
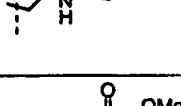
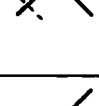
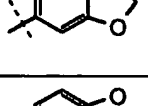
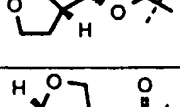
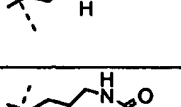
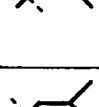
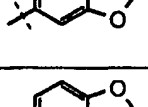
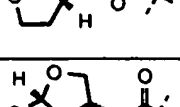
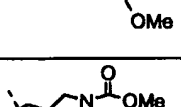
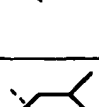
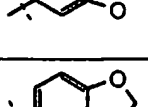
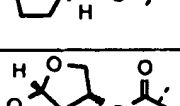
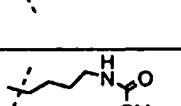
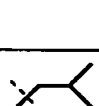
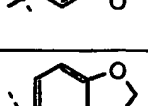
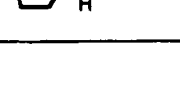
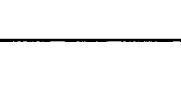
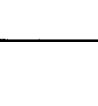
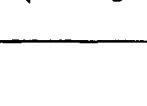
	A	S(O) ₂ E	R ⁸
67			
68			
69			
70			
71			
72			
73			

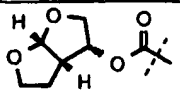
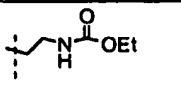
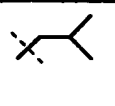
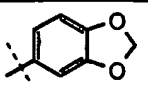
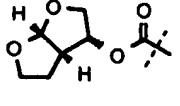
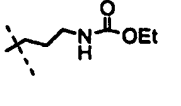
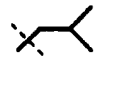
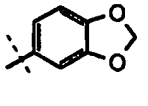
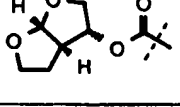
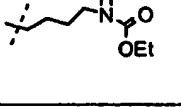
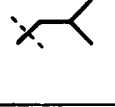
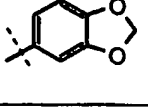
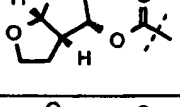
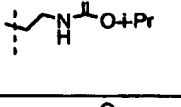
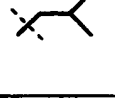
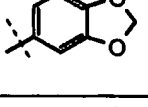
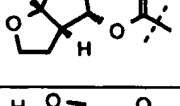
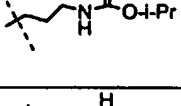
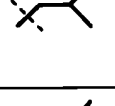
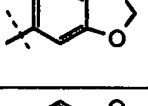
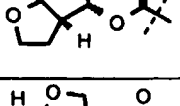
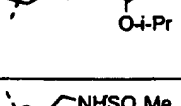
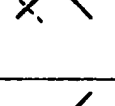
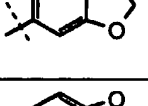
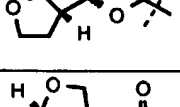
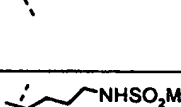
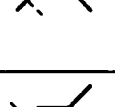
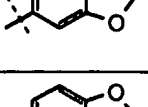
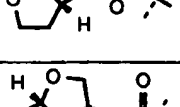
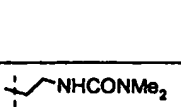
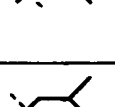
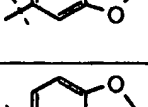
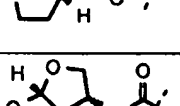
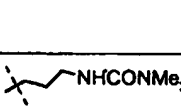
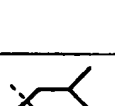
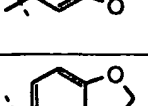
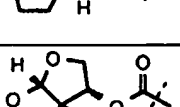
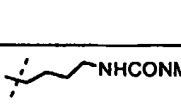
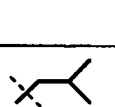
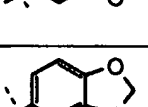
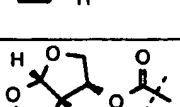
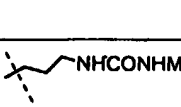
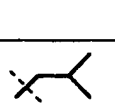
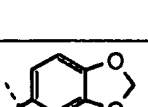
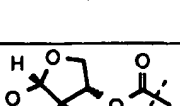
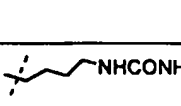
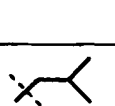
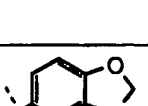
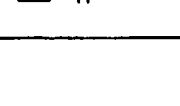
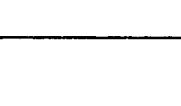


5 Table 3

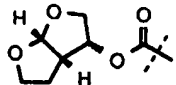


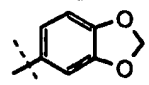
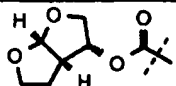


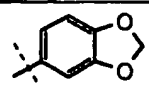
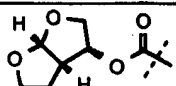
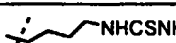

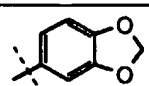
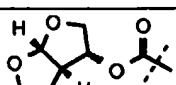
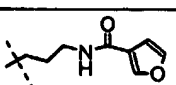

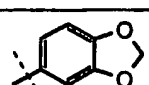
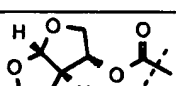
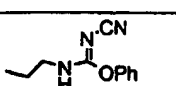

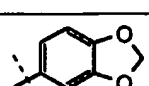
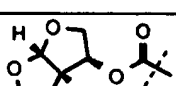
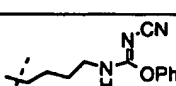

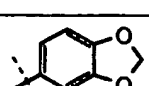
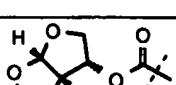
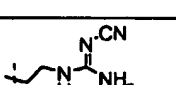

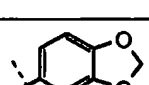
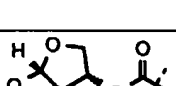
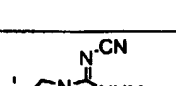

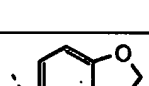
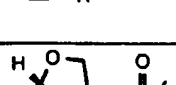
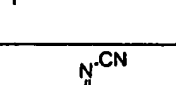

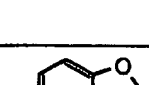
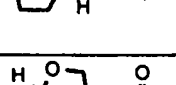
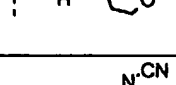


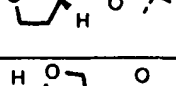
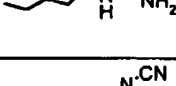

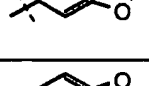
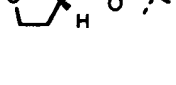
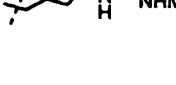

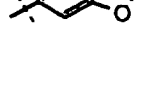
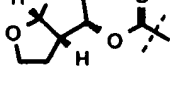
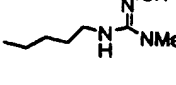

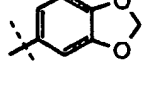
	A	R ⁸	D'	E
201		-H		
202				
203				
204				

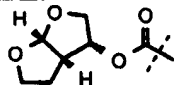
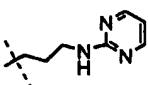

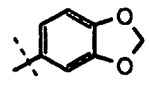
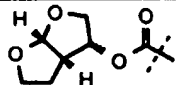
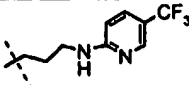

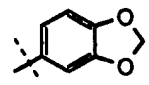
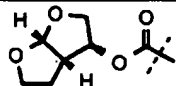
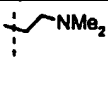

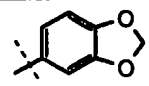
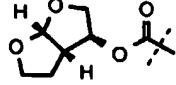
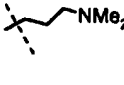

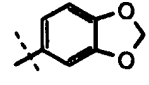
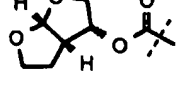
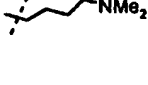

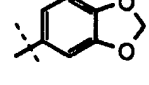
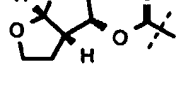


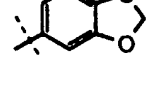
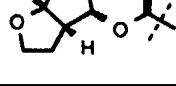


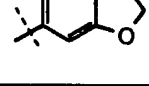
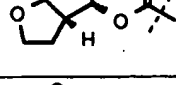


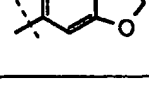
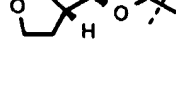
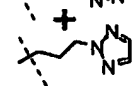

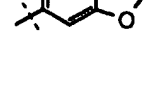
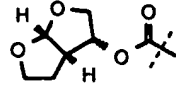
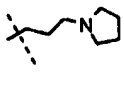

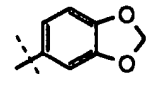
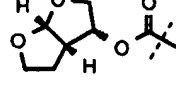
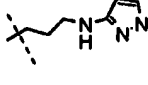

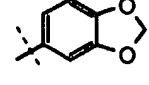
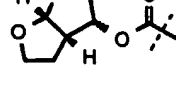
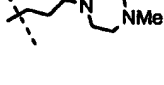

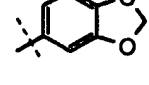
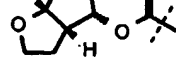


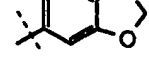
205				
206				
207				
208				
209				
210				
211				
212				
213				
214				
215				
216				
217				

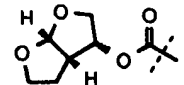
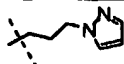

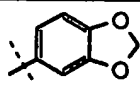
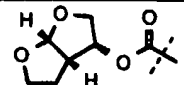
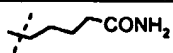

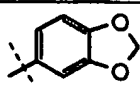
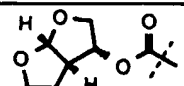
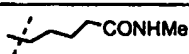

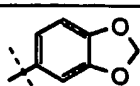
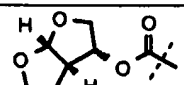
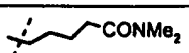

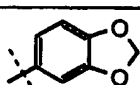
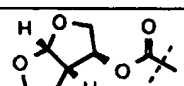
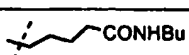

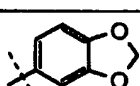
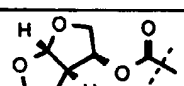
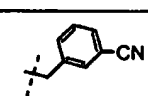

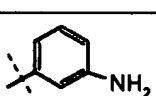
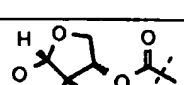
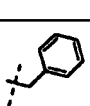

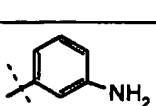
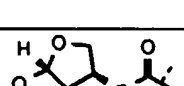

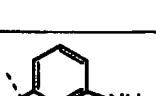
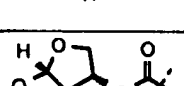
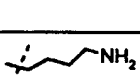


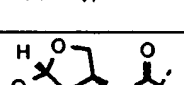
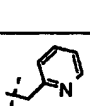


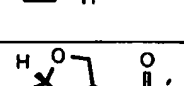
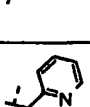

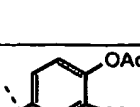
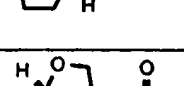
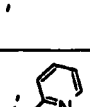

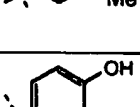
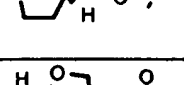
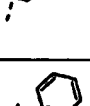

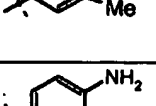
218				
219				
220				
221				
222				
223				
224				
225				
226				
227				
228				
229				
230				
231				

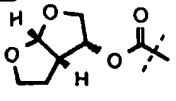
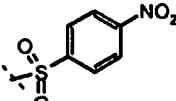

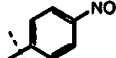
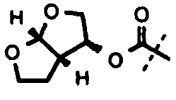
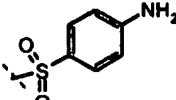


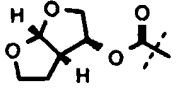


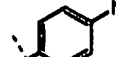
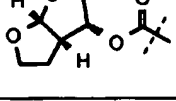
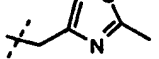

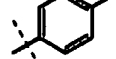
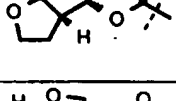
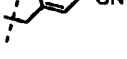

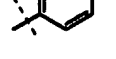
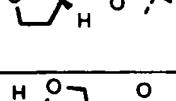


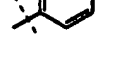
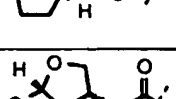
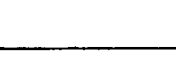





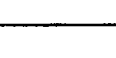
232				
233				
234				
235				
236				
237				
238				
239				
240				
241				
242				
243				
244				

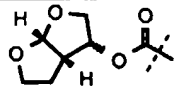

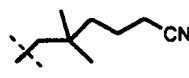
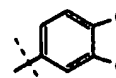
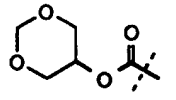

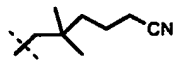
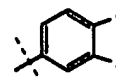
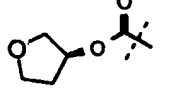

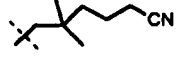
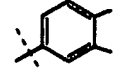
245				
246				
247				
248				
249				
250				
251				
252				
253				
254				
255				
256				
257				

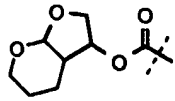


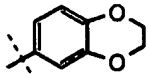
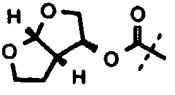

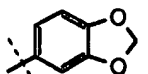
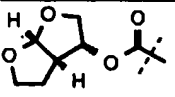

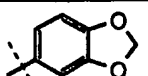
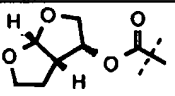

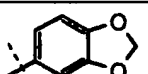
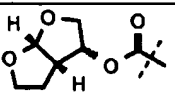

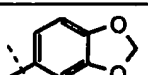
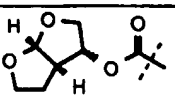
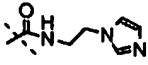

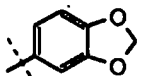
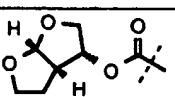


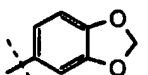
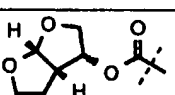


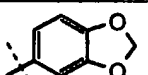
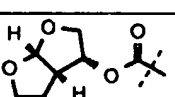
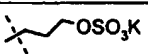

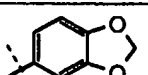
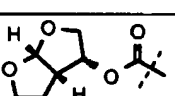


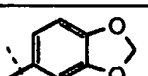
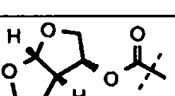
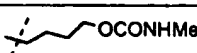

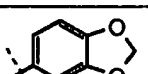
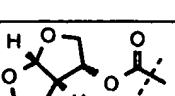
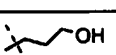


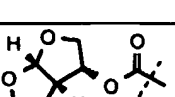
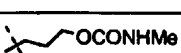


258				
259				
260				
261				
262				
263				
264				
265				
266				
267				
268				
269				
270				

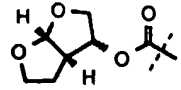
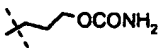

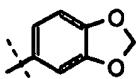
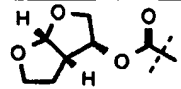


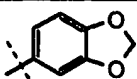
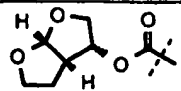
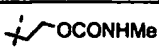

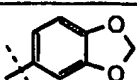
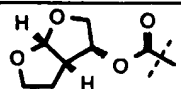
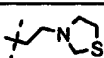

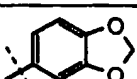
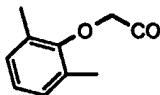


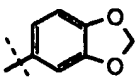
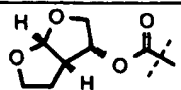
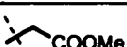

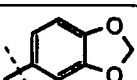
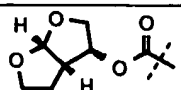
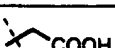

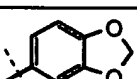
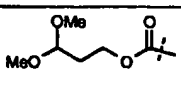


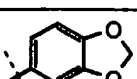
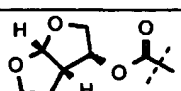

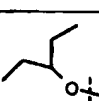
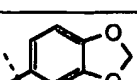
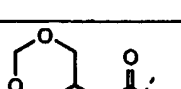

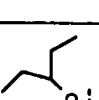

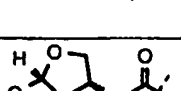
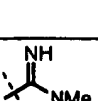


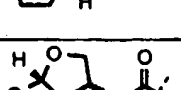
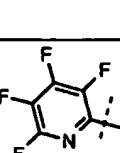

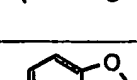
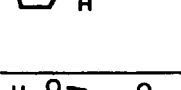
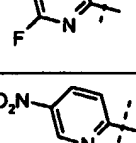


271				
272				
273				
274				
275				
276				
277				
278				
279				
280				
281				
282				
283				

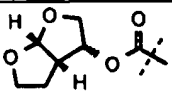
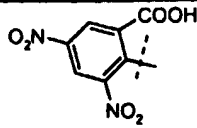

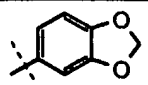
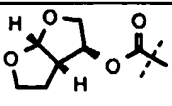
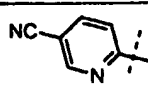

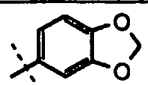
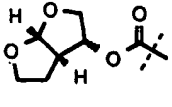
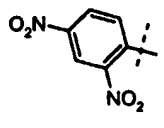

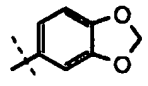
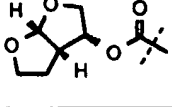


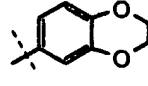
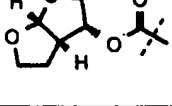
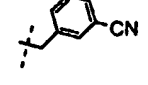

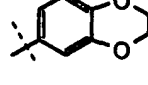
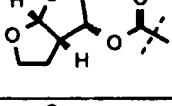
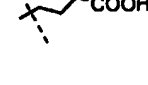

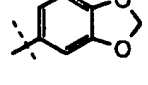
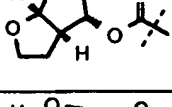


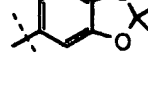
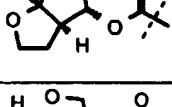


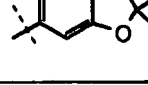
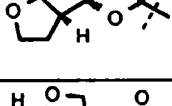
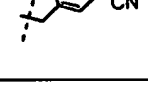

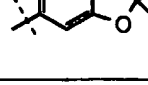
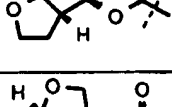


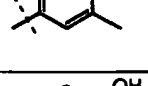
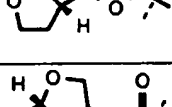


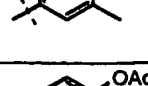
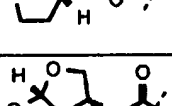


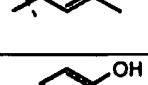
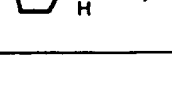



284				
285				
286				
287				
288				
289				
290				
291		H		
292				
293				
294				
295				
296				

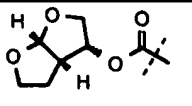
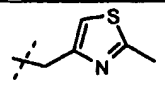
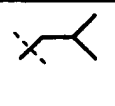
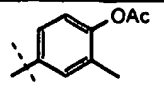
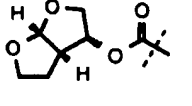
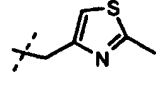
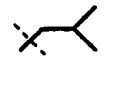
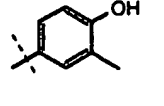
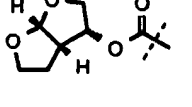
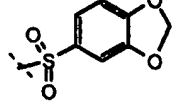
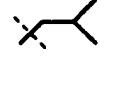
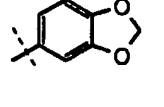
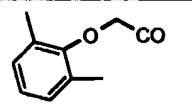
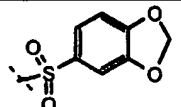
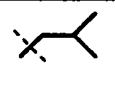
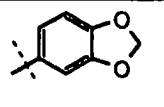
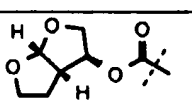
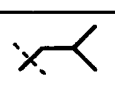
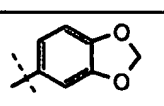
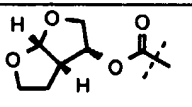
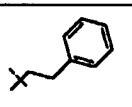
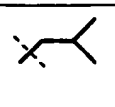
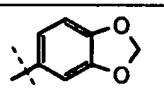
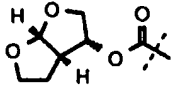
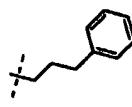
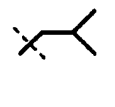
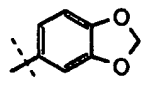
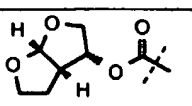
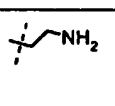
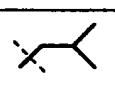
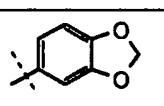
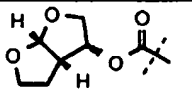
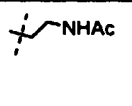
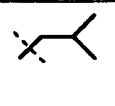
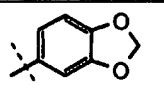
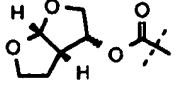
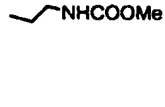
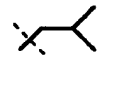
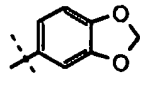
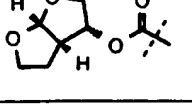
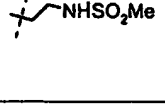
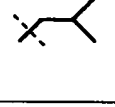
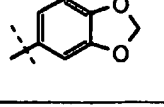
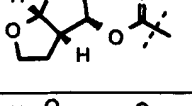
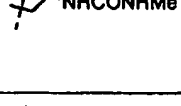
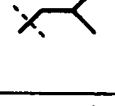
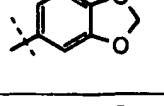
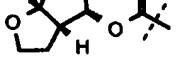
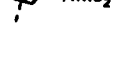
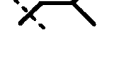
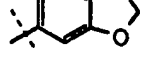
297				
298				
299				
300				
301				
302				
303				
304				

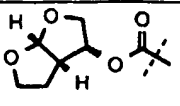

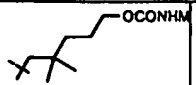
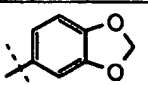
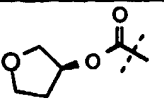

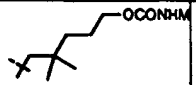
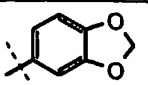
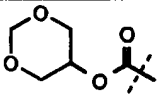

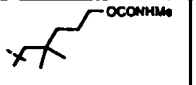
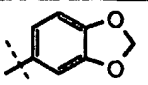
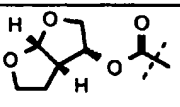

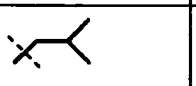
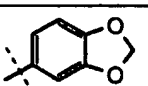
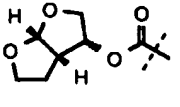

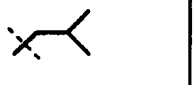
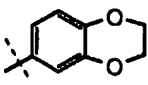
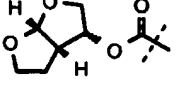
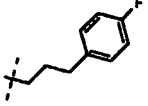
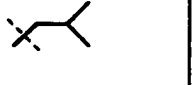
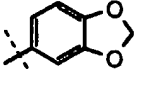
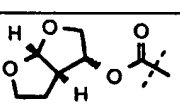
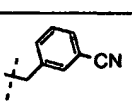
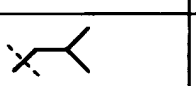
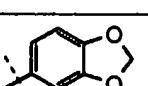
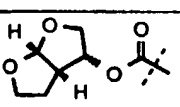
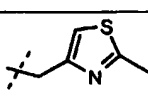
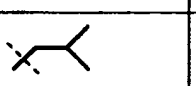
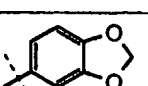
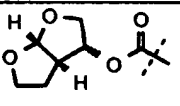
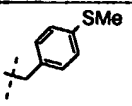
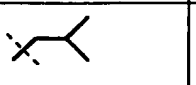
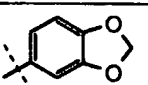
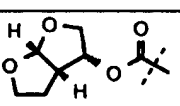
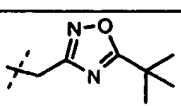
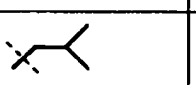
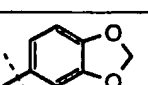
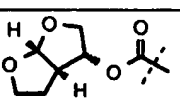
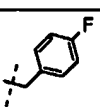
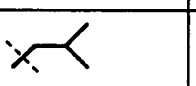
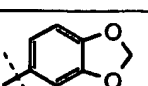
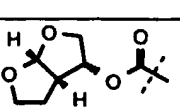
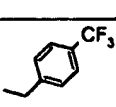
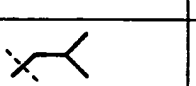
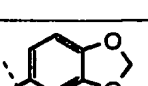
	A	R ^B	D'	E
305				
306				
307				

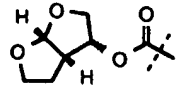
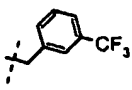
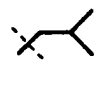
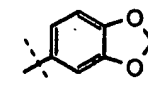
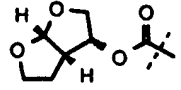
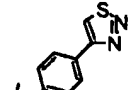
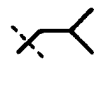
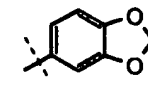
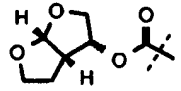
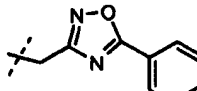
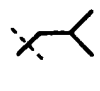
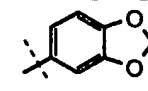
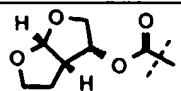
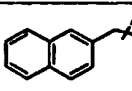
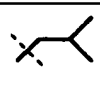
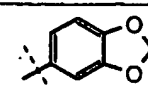
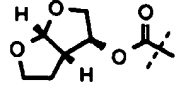
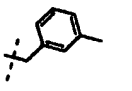
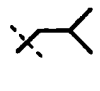
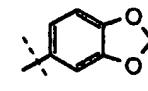
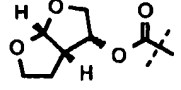
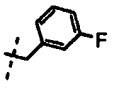
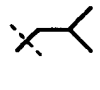
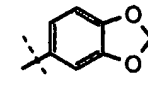
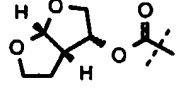
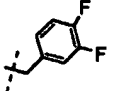
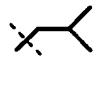
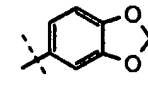
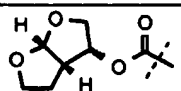
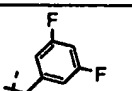
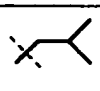
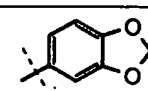
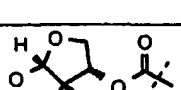
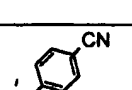
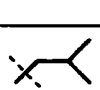
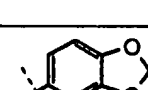
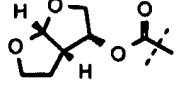
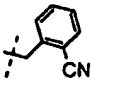
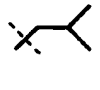
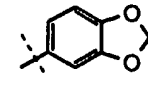
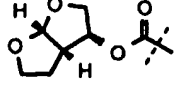
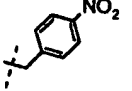
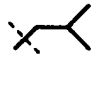
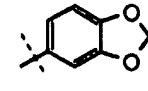
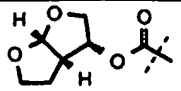
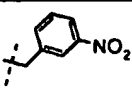
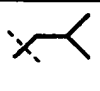
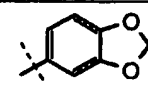
308				
309		-CONHMe		
310		-CONH-i-Pr		
311		-CONMe ₂		
312		-CONH ₂		
313				
314				
315				
316				
317				
318				
319				
320				

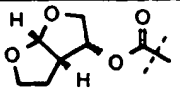
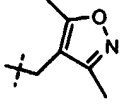

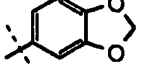
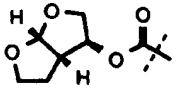
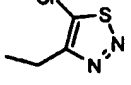

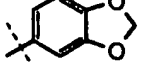
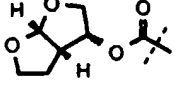
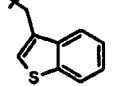


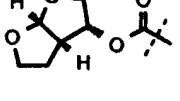
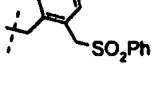

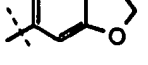
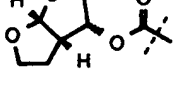
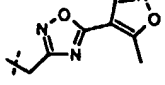

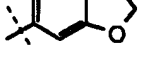
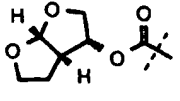
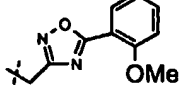

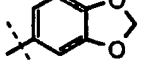
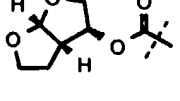
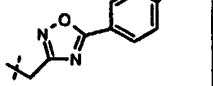


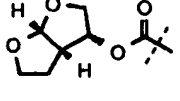
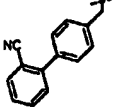


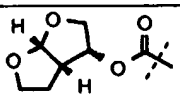


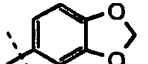
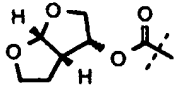
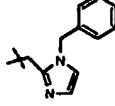

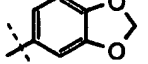
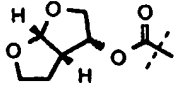

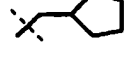
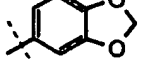
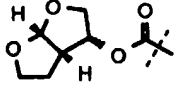
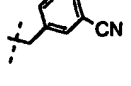

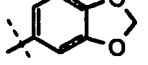
321				
322				
323				
324				
325				
326				
327				
328				
329				
330				
331				
332				
333				

334				
335				
336				
337				
338				
339				
340				
341				
342				
343				
344				
345				
346				

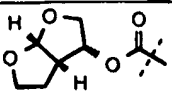

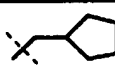
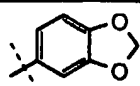
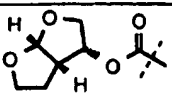

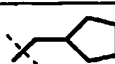
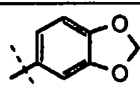
347				
348				
349				
350				
351		H		
352				
353				
354				
355				
356				
357				
358				
359				

361				
362				
363				
364				
365				
366				
367				
368				
369				
370				
371				
372				

373				
374				
375				
376				
377				
378				
379				
380				
381				
382				
383				
384				

385				
386				
387				
388				
389				
390				
391				
392				
393				
394				
395				
396				

-55-

397				
398				

Preferred compound of the present invention are
 compound numbers: 18, 19, 20, 22, 24, 25, 26, 27, 31, 33,
 35, 36, 38, 41, 43, 48, 49, 51, 52, 53, 54, 55, 56, 57,
 5 58, 59, 60, 68, 69, 71, 72, 73, 74, 202-204, 209, 213,
 215, 217, 223, 227, 231, 233, 236, 237, 239, 243, 247,
 250, 260, 263, 271, 281, 289, 293, 295, 304, 309, 317,
 319, 320, 322, 334, 335, 348, 364, 367, 368, 375, 382,
 383 and 396.

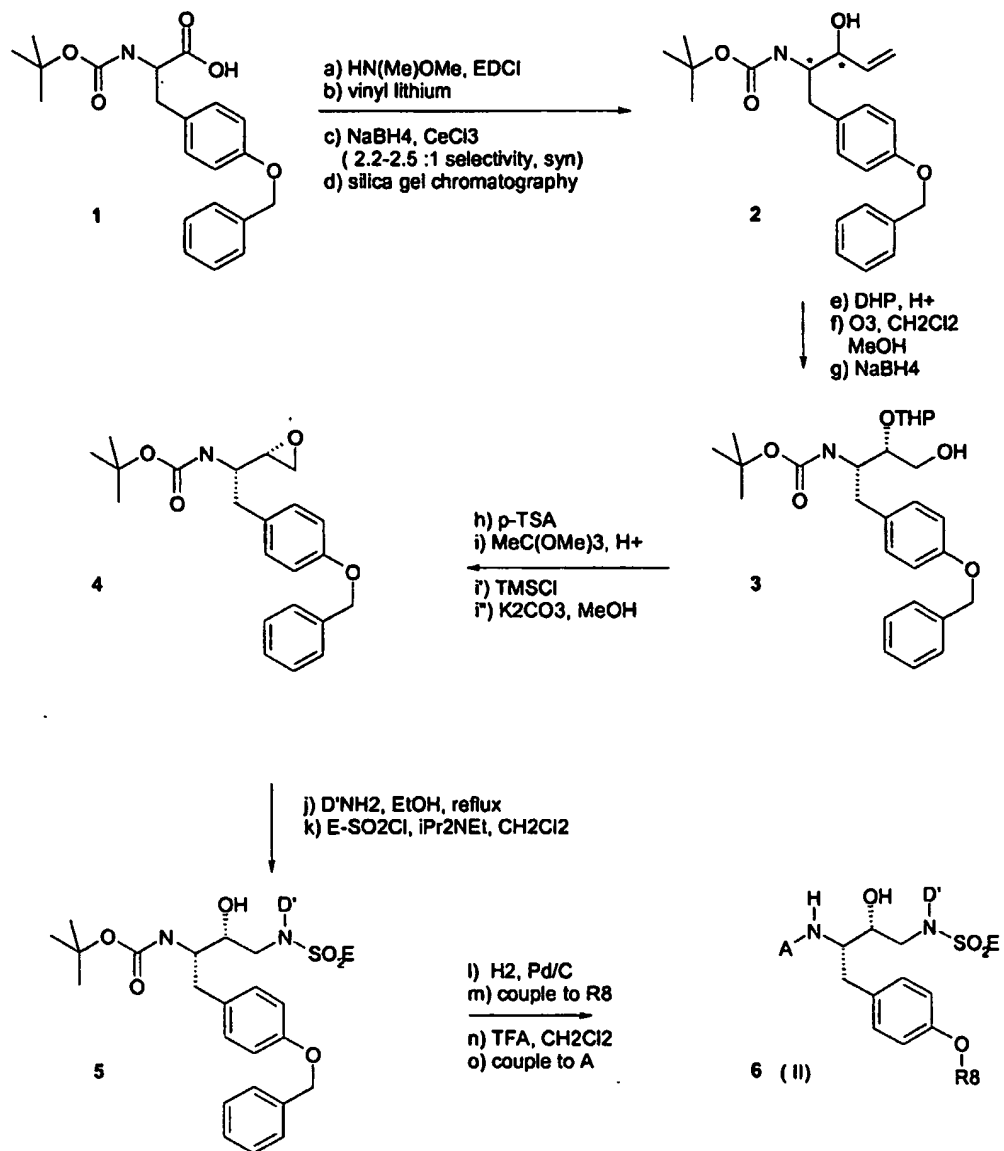
10 More preferred are compound numbers: 26, 27, 31, 33,
 35, 36, 38, 41, 43, 48, 49, 51, 52, 53, 54, 55, 56, 57,
 58, 59, 60, 69, 71, 72, 73, 74, 209, 215, 227, 233, 237,
 281, 289, 295, 304, 309, 322, 335, 364, 368, 382 and 383.

Most preferred are compound numbers: 54, 209, 237,
 15 281, 295, 309, 367 and 368.

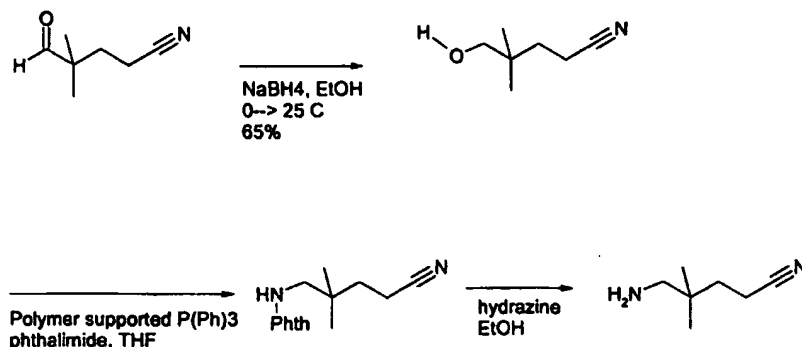
The compounds of the present invention can be
 readily prepared by techniques known in the art. Scheme
 I illustrates a general synthetic route to the compounds
 of this invention.

- 56 -

SCHEME I



SCHEME II



5

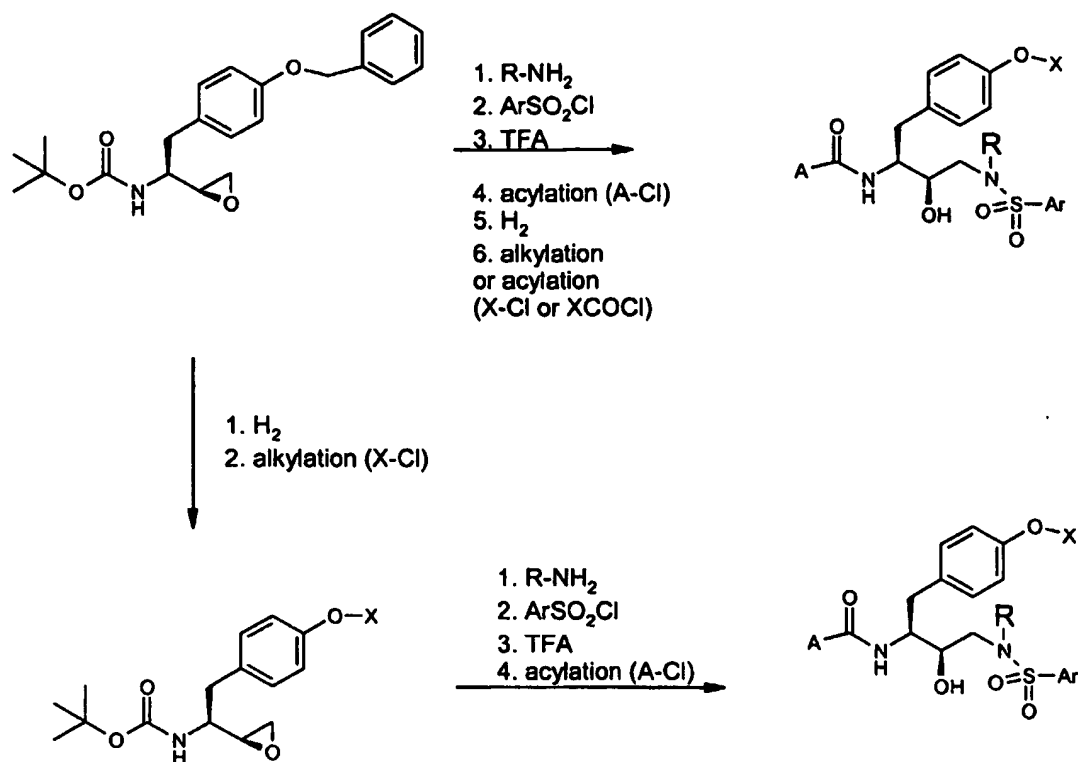
In Step 1 of Scheme I, the bis protected amino acid is homologated through initial conversion to the Wienreb Amide (a) followed by alkylation with vinyl lithium (b) and stereoselective reduction (c). The diastereomers can be separated by silica gel chromatography (d). In step 2, the secondary alcohol is protected as a THP ether (e), as was found necessary for the oxidation step. The olefin was then oxidized to the aldehyde by ozone and the resulting ozonide reduced to the alcohol by sodium borohydride (steps f and g). After removal of the THP group (h) under acidic conditions the diol was converted to the epoxide (i, i' and i'') in one pot according to the method of Sharpless [K. B. Sharpless Tetrahedron 1992, 48 (35), pp. 10515-10530. The epoxide, 4, was then opened by $\text{H}_2\text{N}-\text{D}'$ and further acylated in the presence of $i\text{-Pr}_2\text{Net}$ by $\text{E}-\text{SO}_2\text{Cl}$ to generate compounds of the formula schematically represented as 5. Alternate D' groups may be introduced at this point too. The synthesis of the D' as shown in compounds illustrated in Table II is shown in Scheme II.

These compounds could then be further manipulated by removal of the Bn group and introduction

of a variety of R^8 groups by reacting with the
cooresponding alkyl halides. Further elaboration was
possible by removal of the t-Butyl carbonate (1) and
reintroduction of another group or carbamate designated
5 as A, to provide compounds represented as 6 (formula II).
We found that coupling as in reacton "m" was efficient
under the following general conditions: alkyl halide (R^8 -
Cl, 2.5 EQ. $CsCO_3$, dioxane, $80^\circ C$, 2-4 hours. Similar
alkylating conditions are reported in J. Med. Chem 1992,
10 1688 along with representative routes for the synthesis
of some R^8 -Cl intermediates. The coupling as illustrated
for bringing in A, step "o", was generally efficient
under the following conditions: activated p- NO_2 -phenyl
carbonate (p- NO_2 -O-A), i- Pr_2NEt , CH_2Cl_2 , RT, 12 hours. Use
15 of the activated succinate provides an alternative
coupling reagent (Succinate-A).

Alternatively, compounds of the present invention
can also be prepared according to Scheme III below.

SCHEME III



Thus, the synthetic approach illustrated in Scheme I and Scheme III can be readily extended to produce other compounds of the present invention. The above synthetic schemes are not intended to comprise a comprehensive list of all means by which compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary skill in the art.

As discussed above, the novel compounds of the present invention are excellent ligands for aspartyl proteases, particularly HIV-1 and HIV-2 proteases. Accordingly, these compounds are capable of targeting and inhibiting late stage events in HIV replication, i.e., the processing of the viral polyproteins by HIV encoded proteases. Such compounds inhibit the proteolytic processing of viral polyprotein precursors by inhibiting

aspartyl protease. Because aspartyl protease is essential for the production of mature virions, inhibition of that processing effectively blocks the spread of virus by inhibiting the production of
5 infectious virions, particularly from chronically infected cells. Compounds according to this invention advantageously inhibit the ability of the HIV-1 virus to infect immortalized human T cells over a period of days, as determined by an assay of extracellular p24 antigen --
10 a specific marker of viral replication. Other anti-viral assays have confirmed the potency of these compounds.

The compounds of this invention may be employed in a conventional manner for the treatment of viruses, such as HIV and HTLV, which depend on aspartyl proteases for
15 obligatory events in their life cycle. Such methods of treatment, their dosage levels and requirements may be selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of this invention may be combined with a
20 pharmaceutically acceptable adjuvant for administration to a virally-infected patient in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of the viral infection.

Alternatively, the compounds of this invention may
25 be used in vaccines and methods for protecting individuals against viral infection over an extended period of time. The compounds may be employed in such vaccines either alone or together with other compounds of this invention in a manner consistent with the
30 conventional utilization of protease inhibitors in vaccines. For example, a compound of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in

prophylactically effective amounts to protect individuals over an extended period time against HIV infection. As such, the novel protease inhibitors of this invention can be administered as agents for treating or preventing HIV
5 infection in a mammal.

The compounds of formula I, especially those having a molecular weight of less than about 700 g/mole, may be readily absorbed by the bloodstream of mammals upon oral administration. Compounds of formula I having a
10 molecular weight of less than about 600 g/mole are most likely to demonstrate oral availability. This surprisingly impressive oral availability makes such compounds excellent agents for orally-administered treatment and prevention regimens against HIV infection.

15 The compounds of this invention may be administered to a healthy or HIV-infected patient either as a single agent or in combination with other anti-viral agents which interfere with the replication cycle of HIV. By administering the compounds of this invention with other
20 anti-viral agents which target different events in the viral life cycle, the therapeutic effect of these compounds is potentiated. For instance, the co-administered anti-viral agent can be one which targets early events in the life cycle of the virus, such as cell
25 entry, reverse transcription and viral DNA integration into cellular DNA. Anti-HIV agents targeting such early life cycle events include, didanosine (ddI), alcitabine (ddC), d4T, zidovudine (AZT), polysulfated polysaccharides, sT4 (soluble CD4), ganciclovir,
30 dideoxycytidine, trisodium phosphonoformate, eflornithine, ribavirin, acyclovir, alpha interferon and trimenotrexate. Additionally, non-nucleoside inhibitors of reverse transcriptase, such as TIBO or nevirapine, may be

used to potentiate the effect of the compounds of this invention, as may viral uncoating inhibitors, inhibitors of trans-activating proteins such as tat or rev, or inhibitors of the viral integrase.

5 Combination therapies according to this invention exert a synergistic effect in inhibiting HIV replication because each component agent of the combination acts on a different site of HIV replication. The use of such combinations also advantageously reduces the dosage of a
10 given conventional anti-retroviral agent which would be required for a desired therapeutic or prophylactic effect as compared to when that agent is administered as a monotherapy. These combinations may reduce or eliminate the side effects of conventional single anti-retroviral
15 agent therapies while not interfering with the anti-retroviral activity of those agents. These combinations reduce potential of resistance to single agent therapies, while minimizing any associated toxicity. These combinations may also increase the efficacy of the
20 conventional agent without increasing the associated toxicity. In particular, we have discovered that these compounds act synergistically in preventing the replication of HIV in human T cells. Preferred combination therapies include the administration of a
25 compound of this invention with AZT, ddI, ddC or d4T.

 Alternatively, the compounds of this invention may also be co-administered with other HIV protease inhibitors such as Ro 31-8959 (Roche), L-735,524 (Merck), XM 323 (Du-Pont Merck) and A-80,987 (Abbott) to increase
30 the effect of therapy or prophylaxis against various viral mutants or members of other HIV quasi species.

 We prefer administering the compounds of this invention as single agents or in combination with

retroviral reverse transcriptase inhibitors, such as derivatives of AZT, or other HIV aspartyl protease inhibitors. We believe that the co-administration of the compounds of this invention with retroviral reverse transcriptase inhibitors or HIV aspartyl protease inhibitors may exert a substantial synergistic effect, thereby preventing, substantially reducing, or completely eliminating viral infectivity and its associated symptoms.

10 The compounds of this invention can also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and rEPO); and antibiotics (e.g., pentamidine isethiorate) to prevent or combat infection and disease associated with HIV infections, such as AIDS and ARC.

20 When the compounds of this invention are administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according to this invention may be comprised of a combination of an aspartyl protease inhibitor of this invention and another therapeutic or prophylactic agent.

30 Although this invention focuses on the use of the compounds disclosed herein for preventing and treating HIV infection, the compounds of this invention can also be used as inhibitory agents for other viruses which depend on similar aspartyl proteases for obligatory events in their life cycle. These viruses include, as well as other AIDS-like diseases caused by retroviruses, such as simian immunodeficiency viruses, but are not

limited to, HTLV-I and HTLV-II. In addition, the compounds of this invention may also be used to inhibit other aspartyl proteases, and in particular, other human aspartyl proteases, including renin and aspartyl

5 proteases that process endothelin precursors.

Pharmaceutical compositions of this invention comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable carrier, adjuvant or vehicle.

10 Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin,

15 buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium

20 chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers,

25 polyethylene glycol and wool fat.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral

30 administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The term parenteral as

used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

5 The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting
10 agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable
15 vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed
20 including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated
25 versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Helv or a similar alcohol.

 The pharmaceutical compositions of this invention may be orally administered in any orally acceptable
30 dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating

agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered orally, the active
5 ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for
10 rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active
15 components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily
20 accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the
25 compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a
30 suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl

alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema

5 formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-
10 known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

15 Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between about 0.5 and about 50 mg/kg body weight per day of the active ingredient compound are useful in the prevention and treatment of viral infection, including HIV infection.
20 Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be
25 combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Preferably, such preparations
30 contain from about 20% to about 80% active compound.

Upon improvement of a patient's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if

necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the
5 desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

As the skilled artisan will appreciate, lower or higher doses than those recited above may be required.
10 Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the
15 severity and course of the infection, the patient's disposition to the infection and the judgment of the treating physician.

The compounds of this invention are also useful as commercial reagents which effectively bind to aspartyl
20 proteases, particularly HIV aspartyl protease. As commercial reagents, the compounds of this invention, and their derivatives, may be used to block proteolysis of a target peptide or may be derivatized to bind to a stable resin as a tethered substrate for affinity chromatography
25 applications. These and other uses which characterize commercial aspartyl protease inhibitors will be evident to those of ordinary skill in the art.

As used herein, the compounds according to the invention are defined to include pharmaceutically
30 acceptable derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative" or "pharmaceutically acceptable prodrug" means any pharmaceutically acceptable salt, ester, salt of an

ester, or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an active metabolite or residue thereof. Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

The compounds according to the invention may be used in the form of salts derived from inorganic or organic acids. Included among such acid salts, for example, are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g. sodium), alkaline earth metal (e.g.,

magnesium), ammonium and $^+NW_4$ (wherein W is C_{1-4} alkyl). Physiologically acceptable salts of a hydrogen atom or an amino group include salts of organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, 5 lactobionic and succinic acids; organic sulfonic acids such as methanesulfonic, ethanesulfonic, benzenesulfonic and p-toluenesulfonic acids and inorganic acids such as hydrochloric, sulfuric, phosphoric and sulfamic acids. Physiologically acceptable salts of a compound with a 10 hydroxy group include the anion of said compound in combination with a suitable cation such as Na^+ , NH_4^+ , and NW_4^+ (wherein W is a C_{1-4} alkyl group).

Pharmaceutically acceptable salts include salts of organic carboxylic acids such as ascorbic, acetic, 15 citric, lactic, tartaric, malic, maleic, isothionic, lactobionic, p-aminobenzoic and succinic acids; organic sulphonamic acids such as methanesulphonic, ethanesulphonic, benzenesulphonic and p-toluenesulphonic acids and inorganic acids such as hydrochloric, 20 sulphuric, phosphoric, sulphamic and pyrophosphoric acids.

For therapeutic use, salts of the compounds according to the invention will be pharmaceutically acceptable. However, salts of acids and bases which are 25 non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

Preferred salts include salts formed from hydrochloric, sulfuric, acetic, succinic, citric and 30 ascorbic acids.

Preferred esters of the compounds according to the invention are independently selected from the following groups: (1) carboxylic acid esters obtained by

esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or
5 n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen, C₁₋₄alkyl, or C₁₋₄alkoxy or amino); (2) sulfonate esters, such as alkyl- or
10 aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C₁₋₂₀ alcohol or reactive derivative
15 thereof, or by a 2,3-di (C₆₋₂₄)acyl glycerol.

In such esters, unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms, Any cycloalkyl
20 moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group.

Any reference to any of the above compounds also includes a reference to a pharmaceutically acceptable
25 salts thereof.

The compounds according to the invention are especially useful for the treatment of AIDS and related clinical conditions such as AIDS related complex (ARC), progressive generalized lymphadenopathy (PGL), Kaposi's
30 sarcoma, thrombocytopenic purpura, AIDS-related neurological conditions such as AIDS dementia complex, multiple sclerosis or tropical paraperesis, and also

anti-HIV antibody-positive and HIV-positive conditions, including such conditions in asymptomatic patients.

In a further aspect of the invention there are provided the compounds according to the invention for use
5 in medical therapy particularly for the treatment or prophylaxis of viral infections such as HIV infections.

According to another aspect, the present invention provides a method for the treatment or prevention of the symptoms or effects of a viral
10 infection in an infected animal, for example, a mammal including a human, which comprises treating said animal with a therapeutically effective amount of a compound according to the invention. According to a particular embodiment of this aspect of the invention, the viral
15 infection is an HIV infection. A further aspect of the invention includes a method for the treatment or prevention of the symptoms or effects of an HBV infection.

The compounds according to the invention may also be
20 used in adjuvant therapy in the treatment of HIV infections or HIV-associated symptoms or effects, for example Kaposi's sarcoma.

The present invention further provides a method for the treatment of a clinical condition in an animal,
25 for example, a mammal including a human which clinical condition includes those which have been discussed in the introduction hereinbefore, which comprises treating said animal with a therapeutically effective amount of a compound according to the invention. The present
30 invention also includes a method for the treatment or prophylaxis of any of the aforementioned infections or conditions.

Reference herein to treatment extends to prophylaxis as well as the treatment of established infections or symptoms.

The above compounds according to the invention and their pharmaceutically acceptable derivatives may be employed in combination with other therapeutic agents for the treatment of the above infections or conditions. Combination therapies according to the present invention comprise the administration of at least one compound of the formula (I) or a pharmaceutically acceptable derivative thereof and at least one other pharmaceutically active ingredient. The active ingredient(s) and pharmaceutically active agents may be administered simultaneously in either the same or different pharmaceutical formulations or sequentially in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Preferably the combination therapy involves the administration of one compound according to the invention and one of the agents mentioned herein below.

Examples of such further therapeutic agents include agents that are effective for the treatment of viral infections or associated conditions such as (1 alpha, 2 beta, 3 alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]guanine [(-)BHCG, SQ-34514], oxetanocin-G (3,4-bis-(hydroxymethyl)-2-oxetanosyl]guanine), acyclic nucleosides (e.g. acyclovir, valaciclovir, famciclovir, ganciclovir, penciclovir), acyclic nucleoside phosphonates (e.g. (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC) and PMEA analogs thereof, ribonucleotide reductase inhibitors such as 2-

acetylpyridine 5-[(2-chloroanilino)thiocarbonyl]
thiocarbonohydrazone, 3'-azido-3'-deoxythymidine, other
2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine,
2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, 2',3'-
5 didehydrothymidine, protease inhibitors such as
indinavir, ritonavir, nelfinavir, [3S-[3R*(1R*, 2S*)]]-
[3[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-
hydroxy-1-(phenylmethyl)propyl]-tetrahydro-3-furanyl
ester (141W94), oxathiolane nucleoside analogues such as
10 (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-
cytosine (lamivudine) or cis-1-(2-(hydroxymethyl)-1,3-
oxathiolan-5-yl)-5-fluorocytosine (FTC), 3'-deoxy-3'-
fluorothymidine, 5-chloro-2',3'-dideoxy-3'-fluorouridine,
(-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-
15 cyclopentene-1-methanol, ribavirin, 9-[4-hydroxy-2-
(hydroxymethyl)but-1-yl]-guanine (H2G), tat inhibitors
such as 7-chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2-
(H)one (Ro5-3335), 7-chloro-1,3-dihydro-5-(1H-pyrrol-
2yl)-3H-1,4-benzodiazepin-2-amine (Ro24-7429),
20 interferons such as α -interferon, renal excretion
inhibitors such as probenecid, nucleoside transport
inhibitors such as dipyridamole; pentoxifylline, N-
acetylcysteine (NAC), Procysteine, α -trichosanthin,
phosphonoformic acid, as well as immunomodulators such as
25 interleukin II or thymosin, granulocyte macrophage colony
stimulating factors, erythropoetin, soluble CD₄ and
genetically engineered derivatives thereof, or non-
nucleoside reverse transcriptase inhibitors (NNRTIs) such
as nevirapine (BI-RG-587), zalcitabine (α -APA) and
30 delavuridine (BHAP), and phosphonoformic acid, and 1,4-
dihydro-2H-3,1-benzoxazin-2-ones NNRTIs such as (-)-6-
chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-
dihydro-2H-3,1-benzoxazin-2-one (L-743,726 or DMP-266),

and quinoxaline NNRTIs such as isopropyl (2S)-7-fluoro-3,4-dihydro-2-ethyl-3-oxo-1(2H)-quinoxalinecarboxylate (HBY1293).

More preferably the combination therapy
5 involves the administration of one of the above mentioned agents and a compound within one of the preferred or particularly preferred sub-groups within formula (I) as described above. Most preferably the combination therapy involves the joint use of one of the above named agents
10 together with one of the compounds of formula (I) specifically named herein.

The present invention further includes the use of a compound according to the invention in the manufacture of a medicament for simultaneous or sequential
15 administration with at least one other therapeutic agent, such as those defined herein before.

In order that this invention may be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are
20 not to be construed as limiting the scope of the invention in any way. Compounds for which experimentals are not shown may be made through similar methodologies.

Example 1**Synthesis of BOC Benzyl Tyrosine Based
Weinreb Amide (Scheme 1, Step a)**

5 N-t-BOC-O-Benzyl-L-Tyrosine(1, Sigma) (25 g, 67.3
mmol) was combined with anhydrous DMF (200 ml) and cooled
to 0°C under a N₂ atmosphere. HOBT (15.5 g, 114.4 mmol,
1.7 eq.) and EDC (15.5 g, 80.8 mmol, 1.2 eq.) were added
as solids and stirred to dissolve. Diisopropylethylamine
10 (17.6 ml, 101 mmol, 1.5 eq.) and 4-dimethylaminopyridine
(0.001 g) were added and the reaction was stirred for 50
minutes at 0°C. N,O-Dimethylhydroxylamine
hydrochloride(8.5 g, 87.5 mmol, 1.3 eq.) was added as a
solid and the reaction was stirred for 10 minutes at 0°C
15 then allowed to warm to room temperature and stirred
overnight. After 18 hours at room temperature, the
reaction was cooled to 0°C, and quenched with 200 mL of a
5% sodium bicarbonate solution. The reaction was
extracted twice with EtOAc. The combined organics were
20 washed with five times with water, and then brine, dried
over MgSO₄, filtered and the solvent was removed *in vacuo*.
The yield was 28g of amide which was used as is.
HPLC (5-100% CH₃CN/water) showed 1 peak at 10.77 min and
the NMR (CDCl₃) was consistent with the expected
25 structure.

Example 2**BOC Benzyl Tyrosine derived Vinyl Ketone (Scheme 1, Step
b)**

30 N-t-BOC-O-Benzyl-L-Tyrosine Weinreb amide (18.8 g,
45.3 mmol) was combined with anhydrous THF (200 ml) and
cooled to -78°C. A vinyl lithium solution (2.3 M, 50 ml,

-77-

2.5 eq.) was added via addition funnel dropwise over 20 minutes at -78°C . Ten mL of anhydrous THF was added to rinse the funnel. The reaction was stirred at -78°C under a N_2 atmosphere. HPLC at 1.5 hours showed the
5 reaction was ~50% complete. Another 1.0 eq (20ml) of vinyl lithium was added over 10 minutes at -78°C and washed in with 15mL of THF. The reaction stirred overnight at -78°C . After 18 hours, HPLC showed ~15% Weinreb amide left. Another 0.2 eq (4 ml) of vinyl
10 lithium was added at -78°C . After 26 hours at -78°C , the reaction was quenched with a slow addition of 300mL of 1N HCl. The reaction was partitioned between EtOAc and water. The aqueous phase was extracted with EtOAc. The combined organics were washed consecutively with
15 saturated bicarbonate solution and brine, dried over MgSO_4 , filtered and the solvent was removed in vacuo. The yield was 19.9 g crude material.

The material was purified by flash chromatography (gradient: CH_2Cl_2 to 10%EtOAc/ CH_2Cl_2) to give 13.5g (78%)
20 of pure material. HPLC (5-100% CH_3CN /water) showed 1 peak at 13.37 min and the LC/MS showed 1 peak with an $\text{M}+\text{H} = 382.4$ for the desired compound.

25

Example 3

BOC Benzyl Tyrosine derived Allyl Alcohol (Scheme 1, step c, compound 2)

N-t-BOC-O-benzyl-L-tyrosine vinyl ketone (13.5 g, 35.4 mmol) was combined with methanol (120 ml) and
30 Methylene Chloride (30 mL) and cooled to 0°C . Cerium chloride heptahydrate (14.5 g, 39 mmol, 1.1 eq.) was then added as a solid. The reaction was stirred at 0°C

-78-

for 5 minutes and then cooled to -78°C . A solution of sodium borohydride (2.0 g, 53.1 mmol, 1.5 eq) in 40 mL of MeOH was cooled to -78°C and canulated into the reaction dropwise over 40 minutes. The reaction became a thick
5 white suspension and 50mL of MeOH was added to aid stirring. The reaction was stirred at -78°C for 1.5 hours and was then quenched at -78°C with 150 mL of a saturated ammonium chloride solution. The reaction was extracted three times with EtOAc, and the combined
10 organics were washed with saturated bicarbonate solution, followed by brine, dried over Na_2SO_4 , filtered and the solvent was removed in vacuo to give 13.6 g crude material.

Proton NMR (CDCl_3) shows a 7:3 ratio of
15 diastereomers. The material was purified via chromatography (4:5:1, Hexanes: CH_2Cl_2 :EtOAc) to give 5.4 g of desired material (83:17 ratio of diastereomers) as well as 7.3 g of allyl alcohol as a mix of diastereomers to be repurified. Proton NMR (CDCl_3) was consistent with
20 structure for the desired material.

Example 4

BOC Benzyl Tyrosine Allyl Alcohol

(THP protected) Scheme 1, step e:

25

BOC benzyl tyrosine allyl alcohol (1.59 g, 4.1 mmole) was dissolved in 10 mL of anhydrous CH_2Cl_2 . Dihydropyran (500 μL , 5.4 mmol, 1.3eq.) and pyridinium paratoluenesulfonate (210 mg, 0.8 mmol, 0.2 eq.) was
30 added and the reaction was stirred at room temperature under a N_2 atmosphere. After 19 hours, the solvent was removed in vacuo and the residue was partitioned between

EtOAc and a 10% citric acid solution. The organics were separated, washed with brine, and then saturated bicarbonate solution, dried over Na_2SO_4 , filtered and the solvent was removed in vacuo to give 1.98 g crude material as a white solid.

The material was purified via chromatography (25% EtOAc/Hexanes, (with 0.5ml NEt_3/L)) to give 1.85 g (96%) of desired material. NMR (CDCl_3) was consistent with structure as a mix of diastereomers (1:1) at THP alcohol.

Example 5

BOC Benzyl Tyrosine Diol (THP protected)
(Scheme 1, steps f and g, compound 3)

THP protected BOC benzyl tyrosine allyl alcohol (1.5 g, 3.2 mmol) was dissolved in methanol (5 ml) and methylene chloride (20 mL) and cooled to -78°C . Ozone was bubbled into the stirred solution for 1.5 hours at -78°C . The solution was then flushed with nitrogen to remove the ozone. Sodium borohydride (920 mg, 25.6 mmol, 8 eq.) was then added in small portions over 5 minutes at -78°C . Methanol (35 mL) was added and the reaction was stirred at 78°C for 5 minutes; then was slowly warmed to 0°C . Vigorous bubbling began at -20°C . After 1.5 hours at 0°C the reaction was quenched with saturated bicarbonate solution and extracted with CH_2Cl_2 . The combined organics were washed with brine, dried over Na_2SO_4 , filtered and the solvent was removed in vacuo to give 1.49 g crude material.

The material was purified via chromatography (EtOAc/Hexanes, 20%-30%-40%, containing 0.5ml NEt_3/L) to give 1.15 g (76%) of desired material. HPLC (5-100%

CH₃CN/water) showed 1 peak at 13.81 min and the proton NMR (CDCl₃) was consistent with structure as a mix of diastereomers (~1:1) at the THP alcohol.

5

Example 6**Epoxide (4)**

THP-protected diol (3) (0.40 g, 0.85 mmol) was combined with a catalytic amount of *p*-toluenesulfonic acid (0.004 g) in methanol (20 mL) under a N₂ atmosphere. After stirring at room temperature for ca. 15 minutes, the initial white suspension dissolved completely. Stirring at room temperature was continued for ca. 1 hour, after which time complete disappearance of starting material (3) was confirmed by TLC. The solvent was removed in vacuo to give diol as a white solid, combined with residual *p*-toluenesulfonic acid. The crude diol was dissolved in anhydrous dichloromethane (15 mL), and trimethylorthoacetate (0.130 mL, 1.02 mmol) was added dropwise with stirring. Upon addition of trimethylorthoacetate, the cloudy solution became colourless. After stirring at room temperature for ca. 1 hour, TLC again indicated complete disappearance of starting material. The solvent was removed in vacuo to give the desired cyclic orthoacetate as a viscous white oil, which was re-dissolved in anhydrous DCM (15 mL). Trimethylsilyl chloride (0.129 mL, 1.02 mmol) was added dropwise with stirring. After 1.5 hours at room temperature generally no further starting material remained. The solvent was removed in vacuo to give the desired chloroacetates as a yellow oil, which was dissolved in methanol (20 mL). Cesium carbonate (0.48 g, 1.48 mmol) was added in one portion, and the solution was

stirred at room temperature for 2 hours, after which time, TLC confirmed the absence of any starting material. The solvent was removed in vacuo to give a pale yellow oil, which was partitioned between saturated aqueous ammonium chloride solution (30 mL) and DCM (30 mL). The organic layer was taken, and the aqueous layer re-extracted with DCM (2 x 30 mL). The combined organic extracts were dried over MgSO_4 , and the solvent removed in vacuo to give crude epoxide (4) as a yellow oil. This material was either used in the crude form, or could be purified by flash column chromatography (3:7 ethyl acetate/hexane to 4:1 ethyl acetate/methanol) to give epoxide (4) as a white solid: $R_f = 0.60$ (3:7 ethyl acetate/hexane); ^1H NMR (CDCl_3) 7.49-7.29 (5H, m), 7.14 (2H, d, $J = 8.3$ Hz), 6.93 (2H, d, $J = 8.3$ Hz), 5.05 (2H, s), 4.44 (1H, br. s), 3.64 (1H, br. s), 2.97-2.86 (2H, m), 2.85-2.72 (3H, m), 1.39 (9H, s); coupled LCMS showed the product as a single major peak with m/z 370 $[\text{M}+\text{H}]^+$ or m/z 312 $[\text{M}+\text{H}-t\text{Bu}]^+$ at R_T 2.84 min; HPLC (205 nm) over an extended 20 minute run time showed the crude material to be a 9:1 mixture of diastereoisomeric epoxides at R_T s of 14.2 min. (major diastereoisomer) & 14.3 min. (minor diastereoisomer).

25

Example 7

Isobutylamino Alcohol (Scheme 1, step j)

Crude epoxide (4) (0.37 g, 0.85 mmol) was combined with isobutylamine (large excess, 4 mL) in ethanol (4 mL) under a N_2 atmosphere. The reaction mixture was heated to reflux with stirring for 2.5 hours. The solvent was removed in vacuo to give a pale yellow oily residue. Trituration with hexane gave the isobutylamino alcohol

(0.285 g, 75%) as a white solid: R_f = 0.05 (3:7 ethyl acetate/hexane); ^1H NMR (CDCl_3) 7.47-7.29 (5H, m), 7.15 (2H, d, J = 8.5 Hz), 6.91 (2H, d, J = 8.5 Hz), 5.04 (2H, s), 4.69 (1H, br. d, J = 8.8 Hz), 3.76 (1H, br. s), 3.49-3.40 (1H, m), 2.91 (1H, dd, J = 14.1, 4.7 Hz), 2.87-2.77 (1H, m), 2.67 (2H, d, J = 4.7 Hz), 2.40 (2H, d, J = 6.7 Hz), 1.71 (1H, septet, J = 6.7 Hz), 1.36 (9H, s), 0.91 (3H, d, J = 6.7 Hz), 0.90 (3H, d, J = 6.7 Hz), OH and NH signals not observed; distinct *minor diastereoisomer* signals observed: 4.55 (1H, d, J = 8.7 Hz), 2.49 (2H, d, J = 6.6 Hz); NMR integration showed the triturated product to be a 9:1 mixture of diastereoisomeric isobutylamino alcohols; coupled LCMS showed the product as a single major peak with m/z 443 $[\text{M}+\text{H}]^+$ at R_t 2.41 min.

Example 8

Boc methylenedioxybenzenesulfonamide benzyl ether (Scheme 1, Compound 5e)

Isobutylamino alcohol (0.170 g, 0.38 mmol) was combined with methylenedioxybenzenesulfonyl chloride (0.085 g, 0.38 mmol) in anhydrous DCM (5 mL) under a N_2 atmosphere. The solution was cooled to 0 °C using an ice bath, and diisopropylethylamine (0.20 mL, 1.20 mmol) was added dropwise, and the reaction was allowed to warm to room temperature with stirring for 4 hours. The solvent was removed in vacuo, and the resultant pale yellow oil was purified by flash column chromatography (3:7 ethyl acetate/hexane) to give Boc methylenedioxybenzenesulfonamide benzyl ether (0.185 g, 75%) as a white foam: R_f = 0.30 (3:7 ethyl acetate/hexane); ^1H NMR (CDCl_3) 7.47-7.29 (6H, m), 7.21-7.11 (3H, m), 6.92 (2H, d, J = 8.4 Hz), 6.88 (1H, d, J =

-83-

8.2 Hz), 6.07 (2H, s), 5.04 (2H, s), 4.67-4.58 (1H, m),
3.97-3.85 (1H, m), 3.82-3.56 (2H, m), 3.10-3.02 (2H, m),
2.98-2.72 (4H, m), 1.84 (1H, septet, $J = 6.5$ Hz), 1.36
(9H, s), 0.91 (3H, d, $J = 6.5$ Hz), 0.87 (3H, d, $J = 6.5$
5 Hz); coupled LCMS showed the product as a single major
peak with m/z 627 $[M+H]^+$ at R_T 3.16 min.

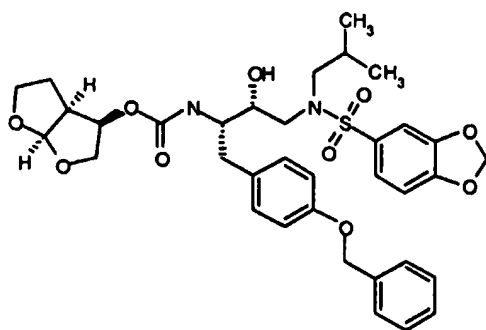
Example 9

Boc *m*-nitrobenzenesulfonamide

10 Benzyl Ether (Scheme 1, Compound 5c)

The isobutylamino alcohol (0.059 g, 0.13 mmol), as
made in Scheme I by the addition of *i*-BuNH₂ to compound 4,
was combined with *m*-nitrobenzenesulfonyl chloride (0.044
15 g, 0.20 mmol) in anhydrous DCM (2 mL) under a N₂
atmosphere. Diisopropylethylamine (0.070 mL, 0.40 mmol)
was added dropwise, and the reaction was stirred at room
temperature for 48 hours. The solvent was removed *in*
vacuo, and the resultant yellow oil was purified by flash
20 column chromatography (3:7 ethyl acetate/hexane) to give
Boc *m*-nitrobenzenesulfonamide benzyl (5) (0.050 g, 61%)
as a colourless oil: $R_f = 0.31$ (3:7 ethyl
acetate/hexane); ¹H NMR (CDCl₃) 8.63 (1H, d, $J = 1.8$ Hz),
8.41 (1H, d, $J = 8.1$ Hz), 8.10 (1H, d, $J = 6.8$ Hz), 7.72
25 (1H, t, $J = 7.9$ Hz), 7.50-7.28 (5H, m), 7.15 (2H, d, $J =$
8.6 Hz), 6.92 (2H, d, $J = 8.6$ Hz), 5.00 (2H, s), 4.65-
4.55 (1H, m), 3.99-3.84 (1H, m), 3.83-3.74 (1H, m), 3.74-
3.64 (1H, m), 3.21 (2H, d, $J = 5.4$ Hz), 3.01 (2H, d, $J =$
7.2 Hz), 2.93-2.80 (2H, m), 1.88 (1H, septet, $J = 6.4$
30 Hz), 1.36 (9H, s), 0.91-0.75 (6H, m).

Example 10

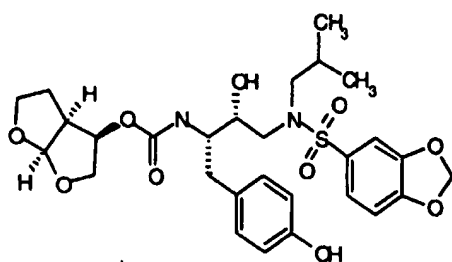


***Bis*-THF methylenedioxybenzenesulfonamide benzyl ether
(46)**

- 5 Boc methylenedioxybenzenesulfonamide benzyl ether (0.040 g, 0.064 mmol) was dissolved in DCM (2 mL). Trifluoroacetic acid (1 mL) was added dropwise, and the reaction was stirred at room temperature for 1 hour. The solvent was removed in vacuo, and the resultant orange
- 10 oil was dissolved in DCM (1.5 mL) and the solution cooled to 0 °C using an ice bath. Diisopropylethylamine (0.33 mL, 1.92 mmol) was added dropwise with stirring, followed by (3R, 3aS, 6aR) hexahydrofuro[2,3-b]furan-2-yl 4-nitrophenyl carbonate (0.021 g, 0.071 mmol) in one
- 15 portion as a solid. After 5 minutes, the ice bath was removed and the reaction mixture was allowed to warm to room temperature with stirring overnight. The solvent was removed in vacuo, and the resultant yellow oil was purified by flash column chromatography (1:1 ethyl
- 20 acetate/hexane) to give *bis*-THF methylenedioxybenzenesulfonamide benzyl ether (46) (0.035 g, 80%) as a white foam: R_f = 0.31 (1:1 ethyl acetate/hexane); ^1H NMR (CDCl_3) 7.45-7.29 (6H, m), 7.17 (1H, d, J = 1.8 Hz), 7.13 (2H, d, J = 8.3 Hz), 6.90 (2H, d, J = 8.3 Hz), 6.94-6.86 (1H, m), 6.07 (2H, s), 5.66 (1H, d, J = 5.2 Hz), 5.10-4.98 (1H, m), 5.02 (2H, s), 4.94 (1H, d, J = 8.5 Hz), 3.96 (1H, dd, J = 9.6, 6.4 Hz),

3.89-3.78 (3H, m), 3.76-3.65 (2H, m), 3.18-3.09 (1H, m),
3.04-2.85 (4H, m), 2.82-2.70 (2H, m), 1.90-1.77 (1H, m),
1.73-1.48 (2H, m), 0.93 (3H, d, $J = 6.5$ Hz), 0.89 (3H, d,
 $J = 6.5$ Hz), OH signal not observed; coupled LCMS showed
5 the product as a single major peak with m/z 683 $[M+H]^+$;
HPLC (205 nm) showed the material as a single major peak
at R_T of 2.73 min. (purity = 96%).

Example 11



10

***Bis*-THF methylenedioxybenzenesulfonamide free phenol (47)**

A solution of *bis*-THF methylenedioxybenzenesulfonamide
benzyl ether (46) (0.022 g, 0.032 mmol) and 10% palladium
15 on carbon (wet; Degussa variant) (0.008 g) in degassed
ethyl acetate (10 mL) was stirred under a balloon of
hydrogen. The reaction was monitored by TLC, and after 20
hours the starting material (47) had not been consumed. A
fresh portion of 10% palladium on carbon (wet; Degussa
20 variant) (0.008 g) was added to the reaction mixture, and
the reaction stirred under a balloon of hydrogen for a
further 4.5 hours. The reaction mixture was filtered
through a pad of celite, and the filtrate was dried *in*
vacuo to give a pale yellow oil. Flash column
25 chromatography (1:1 ethyl acetate/hexane) gave *bis*-THF
methylenedioxybenzenesulfonamide free phenol (47) (0.008
g, 42%) as a colourless oil: $R_f \approx 0.44$ (1:1 ethyl
acetate/hexane); ^1H NMR (CDCl_3); 7.33 (1H, dd, $J = 8.2$,

1.7 Hz), 7.17 (1H, s), 7.07 (2H, d, J = 8.1 Hz), 6.90 (1H, d, J = 8.2 Hz), 6.74 (2H, d, J = 8.1 Hz), 6.09 (2H, s), 5.66 (1H, d, J = 5.2 Hz), 5.10-5.00 (2H, m), 4.05-3.68 (7H, m), 3.18-3.07 (1H, m), 3.06-2.90 (4H, m), 2.87-2.68 (2H, m), 1.89-1.48 (3H, m), 0.93 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.6 Hz); OH signal not observed; coupled LCMS showed the product as a single major peak with m/z 593 $[M+H]^+$; HPLC (205 nm) showed the material as a single major peak at R_T of 1.94 min. (purity = 98%).

10

Example 12

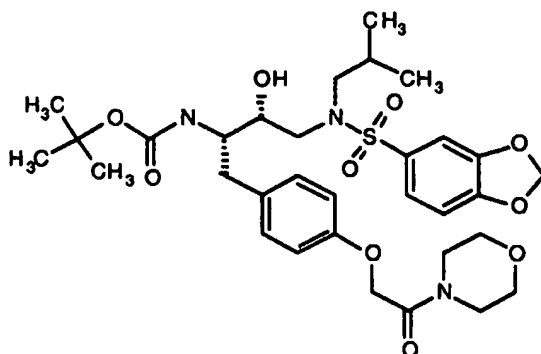
Boc methylenedioxybenzenesulfonamide free phenol (Scheme 1, Compound 6e)

A solution of Boc methylenedioxybenzenesulfonamide benzyl ether (0.063 g, 0.101 mmol) and 10% palladium on carbon (wet; Degussa variant) (0.024 g) in degassed ethyl acetate (10 mL) was stirred under a balloon of hydrogen. The reaction was monitored by TLC, and after 2 hours the starting material had not been consumed. A fresh portion of 10% palladium on carbon (wet; Degussa variant) (0.024 g) was added to the reaction mixture, and the reaction stirred under a balloon of hydrogen for a further 5 hours. The reaction mixture was filtered through a pad of celite, and the filtrate was dried in vacuo to give a colourless oil. Flash column chromatography (1:1 ethyl acetate/hexane) gave Boc methylenedioxybenzenesulfonamide free phenol (6) (0.036 g, 60%) as a white foam: R_f = 0.74 (1:1 ethyl acetate/hexane); 1H NMR ($CDCl_3$); 7.32 (1H, d, J = 8.3 Hz), 7.17 (1H, s), 7.12-7.02 (2H, m), 6.88 (1H, d, J = 8.3 Hz), 6.78-6.69 (2H, m), 6.08 (2H, s), 4.75 (1H, d, J = 8.1 Hz), 3.88-3.62 (3H, m), 3.49 (1H, s), 3.09-3.01 (2H, m), 2.97-2.85 (2H, m), 2.84-2.72 (2H, m), 1.84 (1H, septet, J = 6.6 Hz), 1.37 (9H, s), 0.90 (3H, d, J =

30

-87-

6.6 Hz), 0.86 (3H, d, $J = 6.6$ Hz); coupled LCMS showed the product as a single major peak with m/z 537 $[M+H]^+$ at R_T 2.50 min.

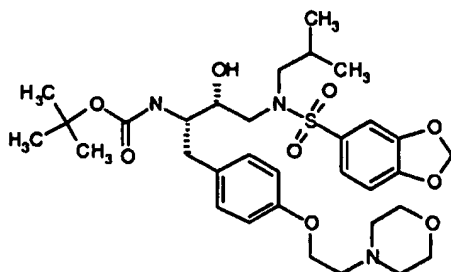
Example 13

**Boc methylenedioxybenzenesulfonamide acetylmorpholine
tethered product (21)**

5

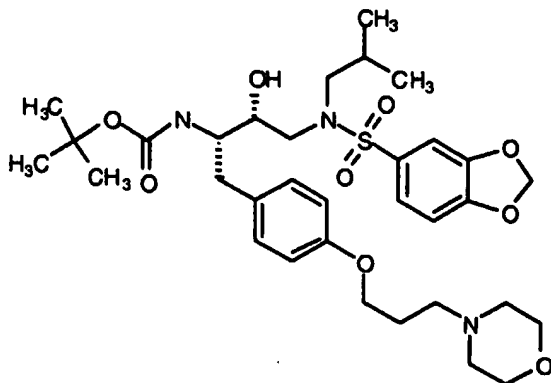
A solution of Boc methylenedioxybenzenesulfonamide free phenol (0.036 g, 0.067 mmol) in 1,4-dioxane (1 mL) was combined with cesium carbonate (0.055 g, 0.168 mmol) and 4-(2-chloroacetyl)morpholine (0.016 g, 0.100 mmol). The solution was heated to 85 °C with stirring for 2 hours, and was cooled and dried in vacuo to give a pale yellow oil. Flash column chromatography (ethyl acetate) gave Boc methylenedioxybenzenesulfonamide acetylmorpholine tethered product (21) (0.032 g, 71%) as a white foam: R_f = 0.51 (ethyl acetate); ^1H NMR (CDCl_3); 7.34 (1H, dd, J = 8.0, 1.7 Hz), 7.22-7.14 (3H, m), 6.93-6.84 (3H, m), 6.09 (2H, s), 4.70-4.59 (1H, m), 4.67 (2H, s), 3.97-3.90 (1H, m), 3.82-3.58 (10H, m), 3.12-3.04 (2H, m), 2.99-2.78 (4H, m), 1.84 (1H, septet, J = 6.6 Hz), 1.36 (9H, s), 0.91 (3H, d, J = 6.6 Hz), 0.88 (3H, d, J = 6.6 Hz); coupled LCMS showed the product as a single major peak with m/z 664 $[\text{M}+\text{H}]^+$; HPLC (205 nm) showed the material as a single major peak at R_t of 2.38 min. (purity = 99%).

25

Example 14

**Boc methylenedioxybenzenesulfonamide ethylmorpholine
5 tethered product (17)**

A solution of Boc methylenedioxybenzenesulfonamide free phenol (0.034 g, 0.063 mmol) in 1,4-dioxane (1 mL) was combined with cesium carbonate (0.052 g, 0.158 mmol) and
10 N-(2-chloroethyl)morpholine (0.014 g, 0.095 mmol). The solution was heated to 85 °C with stirring for 5 hours, and was cooled and dried in vacuo to give a pale yellow oil. Flash column chromatography (4:1 ethyl acetate/hexane) gave Boc methylenedioxybenzenesulfonamide
15 ethylmorpholine tethered product (17) (0.012 g, 29%) as a pale yellow oil: R_f = 0.32 (4:1 ethyl acetate/hexane); ^1H NMR (CDCl_3); 7.32 (1H, dd, J = 8.2, 1.5 Hz), 7.18 (1H, d, J = 1.5 Hz), 7.15 (2H, d, J = 8.3 Hz), 6.88 (1H, d, J = 8.2 Hz), 6.84 (2H, d, J = 8.3 Hz), 6.09 (2H, s), 4.63
20 (1H, d, J = 8.2 Hz), 3.93 (1H, br. s), 3.83-3.64 (7H, m), 3.06 (2H, d, J = 4.9 Hz), 2.98-2.76 (6H, m), 2.68-2.55 (4H, m), 2.54-2.48 (1H, m), 1.84 (1H, septet, J = 6.7 Hz), 1.35 (9H, s), 0.90 (3H, d, J = 6.7 Hz), 0.87 (3H, d, J = 6.7 Hz); coupled LCMS showed the product as a single
25 major peak with m/z 650 $[\text{M}+\text{H}]^+$; HPLC (205 nm) showed the material as a single major peak at R_T of 2.06 min. (purity = 92%).

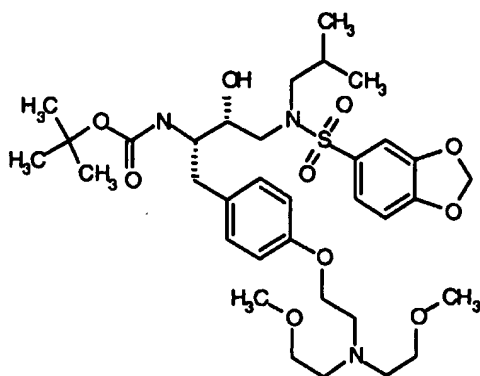
Example 15

5 **Boc methylenedioxybenzenesulfonamide propylmorpholine
tethered product (20)**

A solution of Boc methylenedioxybenzenesulfonamide free phenol (0.038 g, 0.071 mmol) in 1,4-dioxane (1 mL) was
10 combined with cesium carbonate (0.058 g, 0.177 mmol) and
N-(3-chloropropyl)morpholine (0.017 g, 0.107 mmol). The
solution was heated to 85 °C with stirring for 8 hours,
and was cooled and dried in vacuo to give a pale yellow
oil. Flash column chromatography (4:1 ethyl
15 acetate/hexane) gave Boc methylenedioxybenzenesulfonamide
propylmorpholine tethered product (20) (0.006 g, 13%) as
a pale yellow oil: R_f = 0.15 (4:1 ethyl acetate/hexane);
 ^1H NMR (CDCl_3); 7.32 (1H, dd, J = 8.1, 1.8 Hz), 7.19 (1H,
d, J = 1.8 Hz), 7.14 (2H, d, J = 8.4 Hz), 6.88 (1H, d, J
20 = 8.1 Hz), 6.83 (2H, d, J = 8.4 Hz), 6.08 (2H, s), 4.62
(1H, br. s), 4.00 (2H, t, J = 6.3 Hz), 3.84-3.65 (8H, m),
3.61 (2H, t, J = 6.6 Hz), 3.10-3.03 (2H, m), 3.00-2.77
(3H, m), 2.64-2.35 (4H, m), 2.05-1.91 (2H, m), 1.85 (1H,
septet, J = 6.6 Hz), 1.37 (9H, s), 0.90 (3H, d, J = 6.6
25 Hz), 0.87 (3H, d, J = 6.6 Hz); coupled LCMS showed the
product as a single major peak with m/z 664 $[\text{M}+\text{H}]^+$; HPLC

(205 nm) showed the material as a single major peak at R_T of 2.23 min. (purity = 80%).

5

Example 16

Boc methylenedioxybenzenesulfonamide bis-methoxyethylamine tethered product (18)

- 10 A solution of Boc methylenedioxybenzenesulfonamide free phenol (0.034 g, 0.063 mmol) in 1,4-dioxane (1 mL) was combined with cesium carbonate (0.052 g, 0.158 mmol) and freshly prepared 2-[*N,N*-bis-(2-methoxyethyl)amino]ethyl chloride (ca. 0.031 g, ca. 0.016 mmol). The solution was
- 15 heated to 85 °C with stirring for 3.5 hours, and was cooled and dried in vacuo to give a pale yellow oil. Flash column chromatography (ethyl acetate) gave Boc methylenedioxybenzenesulfonamide bis-methoxyethylamine tethered product (18) (0.024 g, 54%) as a white foam: R_f
- 20 = 0.35 (ethyl acetate); ^1H NMR (CDCl_3) 7.32 (1H, dd, J = 8.2, 1.6 Hz), 7.18 (1H, d, J = 1.6 Hz), 7.14 (2H, d, J = 8.5 Hz), 6.88 (1H, d, J = 8.2 Hz), 6.83 (2H, d, J = 8.5 Hz), 6.08 (2H, s), 4.63 (1H, d, J = 7.7 Hz), 4.03 (2H, t, J = 6.1 Hz), 3.92 (1H, br. s), 3.81-3.73 (1H, m), 3.73-
- 25 3.63 (1H, m), 3.50 (4H, t, J = 5.8 Hz), 3.34 (6H, s), 3.10-3.03 (2H, m), 3.01 (2H, t, J = 6.1 Hz), 2.98-2.75

(4H, m), 2.84 (4H, t, $J = 5.8$ Hz), 1.83 (1H, septet, $J = 6.6$ Hz), 1.35 (9H, s), 0.90 (3H, d, $J = 6.6$ Hz), 0.87 (3H, d, $J = 6.6$ Hz); coupled LCMS showed the product as a single major peak with m/z 696 $[M+H]^+$; HPLC (205 nm) showed the material as a single major peak at R_T of 2.20 min. (purity = 100%).

Example 17

10 **Boc methylenedioxybenzenesulfonamide 3-picolyl tethered product (intermediate en route to compound 53)**

A solution of Boc methylenedioxybenzenesulfonamide free phenol (0.010 g, 0.020 mmol) in 1,4-dioxane (1 mL) was combined with cesium carbonate (0.015 g, 0.047 mmol), 3-(chloromethyl)pyridine (ca. 0.004 g, ca. 0.030 mmol; prepared by dissolving 10 mg of 3-(chloromethyl)pyridine hydrochloride in sodium hydroxide (1.5 mL) and diethyl ether (1.5 mL), the organic extract was dried over $MgSO_4$ and the solvent removed in vacuo) and potassium iodide (~1 mg, 0.006 mmol). The solution was heated to 60 °C with stirring for 8 hours, and was cooled and dried in vacuo to give a pale yellow oil. Flash column chromatography (3:7 ethyl acetate/hexane) gave Boc methylenedioxybenzenesulfonamide 3-picolyl tethered product (0.004 g, 34%) as a colourless oil: $R_f = 0.05$ (1:1 ethyl acetate/hexane); coupled LCMS showed the product as a single major peak with m/z 628 $[M+H]^+$ at R_T of 2.27 min.

30

Example 18

Boc methylenedioxybenzenesulfonamide 2-picolyl tethered product (intermediate en route to 52)

A solution of Boc methylenedioxybenzenesulfonamide free
5 phenol (0.010 g, 0.020 mmol) in 1,4-dioxane (1 mL) was
combined with cesium carbonate (0.015 g, 0.047 mmol), 2-
(chloromethyl)pyridine (ca. 0.004 g, ca. 0.030 mmol;
prepared by dissolving 10 mg of 2-(chloromethyl)pyridine
hydrochloride in sodium hydroxide (1.5 mL) and diethyl
10 ether (1.5 mL), the organic extract was dried over MgSO_4
and the solvent removed in vacuo) and potassium iodide
(~1 mg, 0.006 mmol). The solution was heated to 60 °C with
stirring for 8 hours, and was cooled and dried in vacuo
to give a pale yellow oil. Flash column chromatography
15 (3:7 ethyl acetate/hexane) gave Boc
methylenedioxybenzenesulfonamide 2-picolyl tethered
product (0.004 g, 34%) as a colourless oil: R_f = 0.3
(1:1 ethyl acetate/hexane); coupled LCMS showed the
product with m/z 628 $[\text{M}+\text{H}]^+$ at R_T of 2.35 min.

20

Example 19

Boc methylenedioxybenzenesulfonamide 4-picolyl tethered product (intermediate en route to compound 54)

25 A solution of Boc methylenedioxybenzenesulfonamide free
phenol (0.010 g, 0.020 mmol) in 1,4-dioxane (1 mL) was
combined with cesium carbonate (0.015 g, 0.047 mmol), 4-
(chloromethyl)pyridine (ca. 0.004 g, ca. 0.030 mmol;
prepared by dissolving 10 mg of 4-(chloromethyl)pyridine
hydrochloride in sodium hydroxide (1.5 mL) and diethyl
30 ether (1.5 mL), the organic extract was dried over MgSO_4
and the solvent removed in vacuo) and potassium iodide
(~1 mg, 0.006 mmol). The solution was heated to 60 °C with

-94-

stirring for 16 hours, and was cooled and dried in vacuo to give a pale yellow oil. Flash column chromatography (3:7 ethyl acetate/hexane) gave Boc methylenedioxybenzenesulfonamide 4-picolyt tethered product (0.004 g, 34%) as a colourless oil: R_f = 0.10 (2:3 ethyl acetate/hexane); coupled LCMS showed the product with m/z 628 $[M+H]^+$ at R_T of 2.24 min.

Example 20

10 **Boc methylenedioxybenzenesulfonamide 3-methyl-5-methylisoxazole tethered product**
(intermediate en route to compound 55)

A solution of Boc methylenedioxybenzenesulfonamide free phenol (0.010 g, 0.020 mmol) in 1,4-dioxane (1 mL) was combined with cesium carbonate (0.015 g, 0.047 mmol), 3-chloromethyl-5-methyl isoxazole (0.004 g, 0.028 mmol) and potassium iodide (~1 mg, 0.006 mmol). The solution was heated to 60 °C with stirring for 16 hours, and was cooled and dried in vacuo to give a pale yellow oil. Flash column chromatography (3:7 ethyl acetate/hexane) gave Boc methylenedioxybenzenesulfonamide 3-methyl-5-methylisoxazole tethered product (0.005 g, 42%) as a colourless oil: R_f = 0.25 (3:7 ethyl acetate/hexane); 1H NMR ($CDCl_3$) 7.34 (1H, dd, J = 8.4, 1.8 Hz), 7.21-7.13 (3H, m), 6.90 (3H, m), 6.11 (1H, s), 6.09 (2H, s), 5.09 (2H, s), 4.65 (1H, d, J = 8.2 Hz), 3.92 (1H, br. s), 3.82-3.75 (1H, m), 3.73-3.63 (1H, m), 3.09-3.03 (2H, m), 2.98-2.80 (4H, m), 2.43 (3H, s), 1.84 (1H, septet, J = 6.6 Hz), 1.36 (9H, s), 0.91 (3H, d, J = 6.6 Hz), 0.88 (3H, d, J = 6.6 Hz).

Example 21A

Boc methylenedioxybenzenesulfonamide 1-methyl-3,5-dimethylpyrazole tethered product
(intermediate en route to compound 56)

5 A solution of Boc methylenedioxybenzenesulfonamide free phenol (0.010 g, 0.020 mmol) in DMF (1 mL) was combined with anhydrous cesium carbonate (0.015 g, 0.047 mmol). Freshly prepared 1-chloromethyl-3,5-dimethylpyrazole hydrochloride (0.006 g, 0.033 mmol) in DMF (0.5 mL) was
10 added dropwise. The solution was heated to 60 °C with stirring for 15 minutes, and was cooled and dried in vacuo to give a green oil. Flash column chromatography (1:1 ethyl acetate/hexane) gave Boc methylenedioxybenzenesulfonamide 1-methyl-3,5-
15 dimethylpyrazole tethered product (0.002 g, 17%) as a colourless oil: R_f = 0.25 (1:1 ethyl acetate/hexane); coupled LCMS showed the product as a single major peak with m/z 645 $[M+H]^+$ at R_T of 1.68 min.

20

Example 21B

Boc methylenedioxybenzenesulfonamide ethylpyrazole tethered product (intermediate en route to compound 57)

A solution of Boc methylenedioxybenzenesulfonamide free
25 phenol (0.010 g, 0.020 mmol) in acetone (1 mL) was combined with cesium carbonate (0.015 g, 0.047 mmol), 1-(2-chloroethyl)pyrazole (0.004 g, 0.031 mmol) and sodium iodide (~1 mg, 0.007 mmol). The solution was heated to 55 °C with stirring for 60 hours, and was cooled and dried
30 in vacuo to give a yellow oil. Flash column chromatography (1:3 ethyl acetate/hexane) gave Boc methylenedioxybenzenesulfonamide ethylpyrazole tethered product (0.0015 g, 13%) as a colourless oil: R_f = 0.20

-96-

(1:1 ethyl acetate/hexane); coupled LCMS showed the product as a single major peak with m/z 631 $[M+H]^+$ at R_T of 1.65 min.

Example 22**Bis-THF *m*-nitrobenzenesulfonamide Benzyl Ether****(intermediate en route to compounds:25, 34-37)**

5

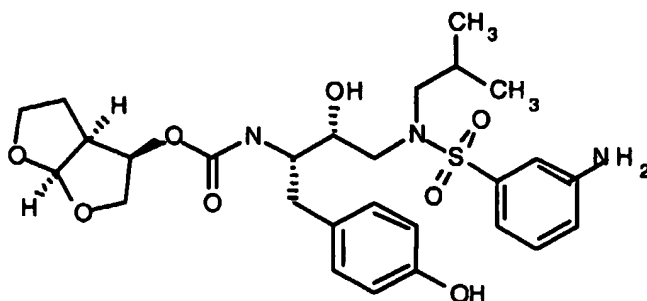
Boc *m*-nitrobenzenesulfonamide benzyl (5c; 0.050 g, 0.08 mmol) was dissolved in DCM (3.4 mL). Trifluoroacetic acid (1.6 mL) was added dropwise, and the reaction was stirred at room temperature for 1 hour. The solvent was removed in vacuo, and the resultant orange oil was dissolved in DCM (1.5 mL) and the solution cooled to 0°C using an ice bath. Diisopropylethylamine (0.42 mL, 2.39 mmol) was added dropwise with stirring, followed by (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-2-yl 4-nitrophenyl carbonate (0.026 g, 0.088 mmol) in one portion as a solid. After 5 minutes, the ice bath was removed and the reaction mixture was allowed to warm to room temperature with stirring overnight. The solvent was removed in vacuo, and the resultant yellow oil was purified by flash column chromatography (1:1 ethyl acetate/hexane) to give bis-THF *m*-nitrobenzenesulfonamide benzyl ether (6; 0.036 g, 66%) as a white foam:

R_f = 0.39 (1:1 ethyl acetate/hexane); ^1H NMR (CDCl_3) 8.62 (1H, d, J = 2.3 Hz), 8.42 (1H, dt, J = 8.1, 0.9 Hz), 8.10 (1H, d, J = 7.7 Hz), 7.73 (1H, t, J = 8.1 Hz), 7.45-7.29 (5H, m), 7.12 (2H, d, J = 8.6 Hz), 6.89 (2H, d, J = 8.6 Hz), 5.65 (1H, d, J = 5.4 Hz), 5.10- 4.98 (1H, m), 5.02 (2H, s), 4.93 (1H, d, J = 8.1 Hz), 3.96 (1H, dd, J = 9.0, 6.3 Hz), 3.91-3.76 (3H, m), 3.76-3.61 (2H, m), 3.24 (1H, dd, J = 15.4, 8.1 Hz), 3.16 (1H, dd, 15.2, 3.0 Hz), 3.06-2.96 (3H, m), 2.96-2.88 (1H, m), 2.74 (1H, dd, J = 14.2, 9.3 Hz), 1.88 (1H, septet, J = 6.7 Hz), 1.73-1.59

(1H, m), 1.59-1.48 (1H, m), 0.90 (6H, t, J = 6.3 Hz), OH signal not observed.

Example 23

5



Bis-THF m-aminophenylsulfonamide Benzyl Ether and Bis-THF m-aminophenylsulfonamide Free Phenol (intermediates en route to compounds 34-37)

10

A solution of bis-THF m-nitrobenzenesulfonamide benzyl ether (5c; 0.036 g, 0.053 mmol) and 10% palladium on carbon (wet Degussa) (0.012 g) in degassed ethyl acetate (15 mL) was stirred under a balloon of hydrogen.

15 The reaction was monitored by TLC, and after 2 hours the starting material had been consumed. An aliquot (5 mL) of the reaction mixture was removed, and filtered through a pad of celite. The filtrate was dried in vacuo to give bis-THF m-aminophenylsulfonamide benzyl ether (compound 20 22) as an off-white oily solid (0.010 g, 29%).

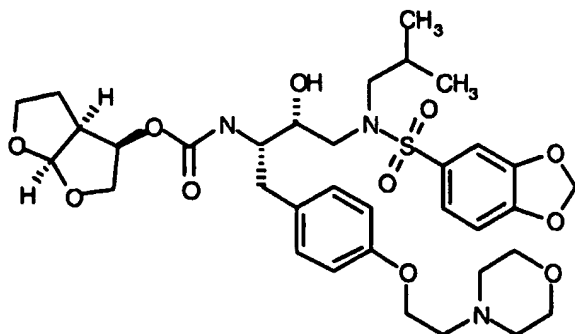
A fresh portion of 10% palladium on carbon (wet Degussa) (0.012 g) was added to the remainder of the reaction mixture, and the reaction stirred under a balloon of hydrogen for a further 2 hours. TLC indicated 25 that an amount of intermediate product remained, so a further portion of 10% palladium on carbon (wet Degussa) (0.012 g) was added to the reaction mixture, and the

-99-

reaction stirred under a balloon of hydrogen overnight.
The reaction mixture was filtered through a pad of
celite, and the filtrate was dried *in vacuo* to give *bis*-
THF *m*-aminophenylsulfonamide free phenol (6: R8 = H, D' =
5 *i*-Bu, E = *m*-NH₂Ph, A = *bis*-THF- CO-) as an off-white oily
solid (0.016g, 54%).

For *bis*-THF *m*-aminophenylsulfonamide benzyl ether: R_f =
0.47 (3:1 ethyl acetate/hexane); ¹H NMR (CDCl₃); 7.45-7.28
10 (7H, m), 7.28-7.19 (1H, m), 7.17-7.08 (3H, m), 6.89 (2H,
d, J = 8.1 Hz), 5.65 (1H, dd, J = 9.3, 5.2 Hz), 5.10-4.95
(4H, m), 4.00-3.60 (6H, m), 3.30-2.80 (6H, m), 2.74 (1H,
dd, J = 10.4, 9.0 Hz), 1.92-1.80 (1H, m), 1.75-1.43 (2H,
m), 0.95-0.88 (6H, m); OH and NH₂ signals not observed;
15 coupled LCMS showed the product as a single major peak
with *m/z* 654 [M+H]⁺; HPLC (205 nm) showed the material to
be split into 2 peaks at R_Ts of 2.33 min. & 2.38 min.
(combined purity = 89%).

20 For *bis*-THF *m*-aminophenylsulfonamide free phenol : D' = *i*-
Bu, E = *m*-NH₂Ph, A = *bis*-THF- CO-, R8 = H): R_f = 0.21
(3:1 ethyl acetate/hexane); ¹H NMR (CDCl₃); 7.28 (1H, dd,
J = 15.3, 7.2 Hz), 7.13-7.10 (1H, m), 7.08 (2H, d, J =
8.1 Hz), 7.03-6.99 (1H, m), 6.86 (1H, dd, J = 7.9, 1.6
25 Hz), 6.75 (2H, d, J = 8.6 Hz), 5.66 (1H, d, J = 4.9 Hz),
5.05 (2H, d, J = 7.7 Hz), 4.01- 3.59 (7H, m), 3.17-3.04
(1H, m), 3.04-2.89 (4H, m), 2.86-2.74 (2H, m), 1.91-1.50
(3H, m), 0.93 (3H, d, J = 6.5 Hz), 0.81 (3H, d, J = 6.5
Hz); OH and NH₂ signals not observed; coupled LCMS showed
30 the product as a single major peak with *m/z* 565 [M+H]⁺;
HPLC (205 nm) showed the material as a single major peak
at R_T of 1.53 min. (purity = 92%).

Example 25

**Bis-THF methylenedioxybenzenesulfonamide
ethylmorpholine tethered product (Compound 48)**

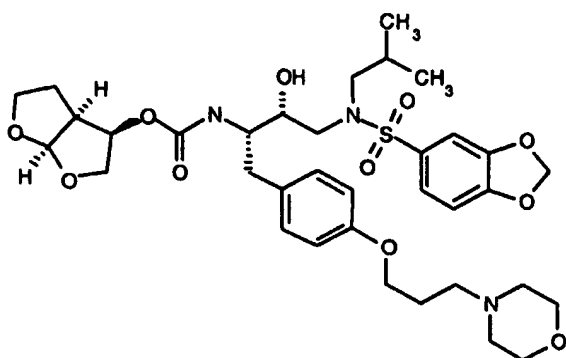
5

Boc methylenedioxybenzenesulfonamide ethylmorpholine
tethered product (Compound 17; 0.011 g, 0.017 mmol) was
dissolved in DCM (1 mL). Trifluoroacetic acid (0.5 mL)
was added dropwise, and the reaction was stirred at room
10 temperature for 1 hour. The solvent was removed in
vacuo, and the resultant orange oil was dissolved in DCM
(0.3 mL) and the solution cooled to 0°C using an ice bath.
Diisopropylethylamine (0.088 mL, 0.51 mmol) was added
dropwise with stirring, followed by (3R, 3aS, 6aR)
15 hexahydrofuro[2,3-b]furan-2-yl 4-nitrophenyl carbonate
(0.006 g, 0.020 mmol) in one portion as a solid. After 5
minutes, the ice bath was removed and the reaction
mixture was allowed to warm to room temperature with
stirring overnight. The solvent was removed in vacuo,
20 and the resultant yellow oil was purified by flash column
chromatography (from 4:1 ethyl acetate/hexane to 9:1
DCM/methanol) to give bis-THF
methylenedioxybenzenesulfonamide ethylmorpholine tethered
product (Compound 48) (0.0095 g, 79%) as a pale yellow
25 oil: R_f = 0.50 (9:1 DCM/methanol); ^1H NMR (CDCl_3) 7.40-
7.28 (1H, m), 7.23-7.04 (3H, m), 6.97-6.87 (1H, m), 6.87-
6.77 (2H, m), 6.12 (2H, s), 5.68 (1H, d, J = 4.8 Hz),

-101-

5.11-5.00 (1H, m), 5.00-4.87 (1H, m), 4.03-3.92 (2H, m),
3.92-3.53 (10H, m), 3.21-3.07 (2H, m), 3.07-2.92 (3H, m),
2.92-2.74 (4H, m), 2.74-2.54 (4H, m), 1.96-1.37 (3H, m),
1.02-0.78 (6H, m), OH signal not observed; coupled LCMS
5 showed the product as a single major peak with m/z 706
[M+H]⁺; HPLC (205 nm) showed the material as a single
major peak at R_T of 1.83 min. (purity = 95%).

Example 26



10

**Bis-THF methylenedioxybenzenesulfonamide
propylmorpholine tethered product (Compound 49)**

Boc methylenedioxybenzenesulfonamide
15 propylmorpholine tethered product (20) (0.006 g, 0.009
mmol) was dissolved in DCM (1 mL). Trifluoroacetic acid
(0.5 mL) was added dropwise, and the reaction was stirred
at room temperature for 1 hour. The solvent was removed
in vacuo, and the resultant orange oil was dissolved in
20 DCM (0.3 mL) and the solution cooled to 0°C using an ice
bath. Diisopropylethylamine (0.047 mL, 0.27 mmol) was
added dropwise with stirring, followed by (3R, 3aS, 6aR)
hexahydrofuro[2,3-b]furan-2-yl 4-nitrophenyl carbonate
(0.003 g, 0.011 mmol) in one portion as a solid. After 5
25 minutes, the ice bath was removed and the reaction
mixture was allowed to warm to room temperature with

stirring overnight. The solvent was removed in vacuo, and the resultant yellow oil was purified by flash column chromatography (from 4:1 ethyl acetate/hexane to 9:1 DCM/methanol) to give *bis*-THF

- 5 methylenedioxybenzenesulfonamide propylmorpholine tethered product (Compound 49) (0.0045 g, 69%) as a yellow oil: R_f = 0.50 (9:1 DCM/methanol); ^1H NMR (CDCl_3) 7.36-7.30 (1H, m), 7.19 (1H, s), 7.13 (2H, d, J = 8.4 Hz), 6.91 (1H, d, J = 8.3 Hz), 6.82 (2H, d, J = 8.3 Hz),
10 6.11 (2H, s), 5.67 (1H, d, J = 5.1 Hz), 5.19-5.08 (1H, dd, J = 13.6, 6.1 Hz), 4.92 (1H, d, J = 9.0 Hz), 4.07-3.92 (4H, m), 3.92-3.65 (8H, m), 3.19-3.08 (1H, m), 3.05-2.85 (4H, m), 2.85-2.71 (2H, m), 2.71-2.43 (6H, m), 2.13-1.94 (2H, m), 1.94-1.77 (1H, m), 1.77-1.49 (2H, m), 0.95
15 (3H, d, J = 6.5 Hz), 0.90 (3H, d, J = 6.7 Hz), OH signal not observed; coupled LCMS showed the product as a single major peak with m/z 720 $[\text{M}+\text{H}]^+$; HPLC (205 nm) showed the material as a single major peak at R_T of 1.90 min. (purity = 93%).

20

Example 27

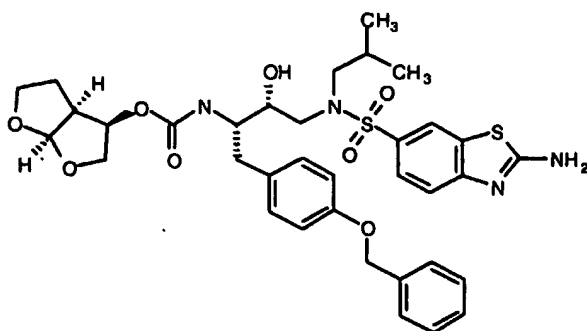
Boc Benzothiazole Sulfonamide Benzyl Ether (Compound 5g, Scheme 1)

25

- The isobutylamino alcohol (0.50 g, 1.13 mmol) was combined with 2-aminobenzothiazole-6- sulfonyl chloride (0.373 g, 1.50 mmol) in anhydrous DCM (10 mL) under a N_2 atmosphere. Diisopropylethylamine (0.59 mL, 3.39 mmol)
30 was added dropwise, and the reaction was stirred at room temperature for 42 hours. The solvent was removed in vacuo, and the resultant yellow oil was purified by flash column chromatography (4:1 ethyl acetate/hexane) to give

Boc benzothiazole sulfonamide benzyl ether (5: D' = i-Bu, E = 2-aminobenzothiazole) (0.30 g, 42%) as a white solid: R_f = 0.60 (4:1 ethyl acetate/hexane); ^1H NMR (CDCl_3) 8.05 (1H, d, J = 1.8 Hz), 7.72 (1H, dd, J = 8.6, 1.8 Hz), 7.60 (1H, d, J = 8.6 Hz), 7.49-7.32 (5H, m), 7.19 (2H, d, J = 8.6 Hz), 6.94 (2H, d, J = 8.6 Hz), 5.67 (2H, br.s, NH_2), 5.07 (2H, s), 4.70 (1H, br.d, J = 7.7 Hz), 4.00 (1H, br.s, OH), 3.89-3.80 (1H, m), 3.80-3.66 (1H, m), 3.23-3.06 (2H, m), 3.06-2.77 (4H, m), 1.89 (1H, septet, J = 7.2 Hz), 1.38 (9H, s), 0.94 (3H, d, J = 6.3 Hz), 0.90 (3H, d, J = 6.3 Hz).

Example 28

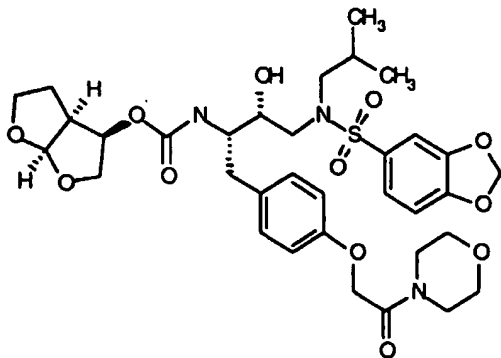


**Bis-THF benzothiazolesulfonamide
Benzyl Ether (Compound 44)**

Boc benzothiazole sulfonamide benzyl ether (Compound 5, Scheme 1: D' = i-Bu, E = 2-aminobenzothiazole) (0.30 g, 0.46 mmol) was dissolved in DCM (10 mL). Trifluoroacetic acid (5 mL) was added dropwise, and the reaction was stirred at room temperature for 1 hour. The solvent was removed *in vacuo*, and the resultant orange oil was dissolved in DCM (15 mL). Triethylamine (1.28 mL, 9.20 mmol) was added dropwise with stirring, followed by (3R, 3aS, 6aR) hexahydrofuro[2,3-*b*]furan-2-yl 4-nitrophenyl

carbonate (0.149 g, 0.50 mmol) in one portion as a solid. The reaction mixture was allowed to stir at room temperature overnight. The solvent was removed in vacuo, and the resultant yellow oil was purified by flash column chromatography (ethyl acetate) to give *bis*-THF benzothiazole sulfonamide benzyl ether (Compound 44) (0.158 g, 48%) as a white solid: R_f = 0.50 (ethyl acetate); ^1H NMR (CDCl_3) 8.03 (1H, s), 7.71 (1H, d, J = 8.6 Hz), 7.58 (1H, d, J = 8.6 Hz), 7.48-7.32 (5H, m), 7.15 (2H, d, J = 8.1 Hz), 6.91 (2H, d, J = 8.6 Hz), 5.93 (2H, br.s, NH_2), 5.67 (1H, d, J = 5.4 Hz), 5.16 (1H, d, J = 8.6 Hz), 5.04 (2H, s), 4.05-3.60 (7H, m), 3.27-3.15 (1H, m), 3.12-2.97 (4H, m), 2.97-2.83 (2H, m), 2.78 (1H, dd, J = 14.3, 8.8 Hz), 1.95-1.48 (3H, m), 0.96 (3H, d, J = 6.8 Hz), 0.92 (3H, d, J = 6.8 Hz); coupled LCMS showed the product as a single major peak with m/z 712 $[\text{M}+\text{H}]^+$; HPLC (205 nm) showed the material as a single major peak at R_T of 2.26 min. (purity = 100%).

20

Example 29

***Bis*-THF methylenedioxybenzenesulfonamide acetylmorpholine tethered product (50)**

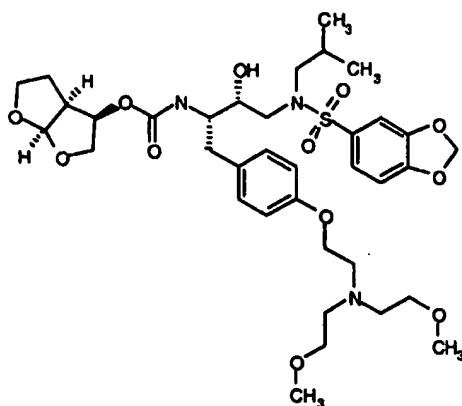
25 Boc methylenedioxybenzenesulfonamide acetylmorpholine tethered product (21) (0.027 g, 0.041 mmol) was dissolved

-105-

in DCM (2 mL). Trifluoroacetic acid (1 mL) was added dropwise, and the reaction was stirred at room temperature for 1 hour. The solvent was removed in vacuo, and the resultant orange oil was dissolved in DCM (1.5 mL) and the solution cooled to 0 °C using an ice bath. Diisopropylethylamine (0.21 mL, 1.22 mmol) was added dropwise with stirring, followed by (3R, 3aS, 6aR) hexahydrofuro[2,3-b]furan-2-yl 4-nitrophenyl carbonate (0.013 g, 0.045 mmol) in one portion as a solid. After 5 minutes, the ice bath was removed and the reaction mixture was allowed to warm to room temperature with stirring overnight. The solvent was removed in vacuo, and the resultant yellow oil was purified by flash column chromatography (ethyl acetate to methanol) to give bis-THF methylenedioxybenzenesulfonamide acetylmorpholine tethered product (50) (0.011 g, 38%) as a yellow foam: R_f = 0.10 (ethyl acetate); ^1H NMR (CDCl_3) 7.33 (1H, d, J = 8.1 Hz), 7.20-7.08 (3H, m), 6.94-6.83 (3H, m), 6.09 (2H, s), 5.72-5.61 (1H, m), 5.10-4.97 (2H, m), 4.67 (2H, s), 4.02-3.92 (1H, m), 3.91-3.77 (3H, m), 3.76-3.56 (10H, m), 3.19-3.07 (1H, m), 3.06-2.88 (4H, m), 2.87-2.71 (2H, m), 1.89-1.75 (1H, m), 1.74-1.62 (1H, m), 1.61-1.48 (1H, m), 0.93 (3H, d, J = 6.6 Hz), 0.89 (3H, d, J = 6.6 Hz), OH signal not observed; coupled LCMS showed the product as a single major peak with m/z 720 $[\text{M}+\text{H}]^+$; HPLC (205 nm) showed the material as a single major peak at R_T of 2.02 min. (purity = 88%).

30

Example 32

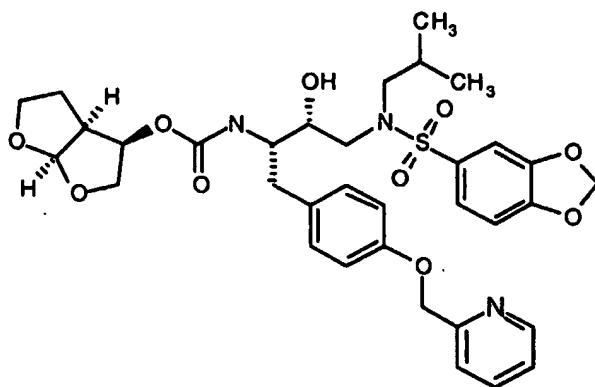


***Bis*-THF methylenedioxybenzenesulfonamide *bis*-methoxyethylamine tethered product (51)**

- 5 Boc methylenedioxybenzenesulfonamide *bis*-methoxyethylamine tethered product (18) (0.023 g, 0.033 mmol) was dissolved in DCM (1 mL). Trifluoroacetic acid (0.5 mL) was added dropwise, and the reaction was stirred at room temperature for 1 hour. The solvent was removed
- 10 *in vacuo*, and the resultant orange oil was dissolved in DCM (1 mL) and the solution cooled to 0 °C using an ice bath. Diisopropylethylamine (0.173 mL, 0.99 mmol) was added dropwise with stirring, followed by (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-2-yl 4-nitrophenyl carbonate
- 15 (0.012 g, 0.040 mmol) in one portion as a solid. After 5 minutes, the ice bath was removed and the reaction mixture was allowed to warm to room temperature with stirring overnight. The solvent was removed *in vacuo*, and the resultant yellow oil was purified by flash column
- 20 chromatography (4:1 ethyl acetate/hexane to ethyl acetate to 9:1 DCM/methanol) to give *bis*-THF methylenedioxybenzenesulfonamide *bis*-methoxyethylamine tethered product (51) (0.022 g, 89%) as a yellow foam: R_f = 0.50 (9:1 DCM/methanol); ^1H NMR (CDCl_3) 7.33 (1H, dd, J = 8.2, 1.8 Hz), 7.17 (1H, d, J = 1.8 Hz), 7.13 (2H, d, J
- 25

= 8.6 Hz), 6.89 (1H, d, J = 8.2 Hz), 6.80 (2H, d, J = 8.6 Hz), 6.09 (2H, s), 5.65 (1H, d, J = 5.2 Hz), 5.08-4.98 (2H, m), 4.35-4.24 (2H, m), 4.00-3.90 (1H, m), 3.90-3.63 (6H, m), 3.61-3.49 (2H, m), 3.42-3.31 (2H, m), 3.35 (6H, s), 3.16-3.07 (2H, m), 3.05-2.88 (4H, m), 2.88-2.74 (2H, m), 1.83 (1H, septet, J = 6.6 Hz), 1.74-1.54 (1H, m), 1.48-1.35 (5H, m), 0.92 (3H, d, J = 6.6 Hz), 0.88 (3H, d, J = 6.6 Hz), OH signal not observed; coupled LCMS showed the product as a single major peak with m/z 752 $[M+H]^+$;
10 HPLC (205 nm) showed the material as a single major peak at R_T of 1.92 min. (purity = 91%).

Example 33



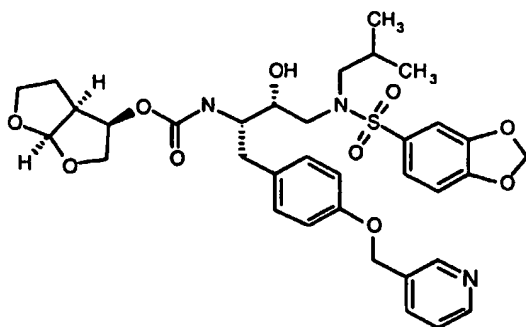
15

**Bis-THF methylenedioxybenzenesulfonamide 2-picolyl
tethered product (53)**

Boc methylenedioxybenzenesulfonamide 2-picolyl tethered
20 product (0.004 g, 0.006 mmol) was dissolved in DCM (0.6 mL). Trifluoroacetic acid (0.3 mL) was added dropwise, and the reaction was stirred at room temperature for 45 minutes. The solvent was removed in vacuo, and the resultant orange oil was dissolved in DCM (1.5 mL).
25 Diisopropylethylamine (0.060 mL, 0.33 mmol) was added dropwise with stirring at room temperature, followed by

(3R, 3aS, 6aR) hexahydrofuro[2,3-b]furan-2-yl 4-nitrophenyl carbonate (0.005 g, 0.017 mmol) in one portion as a solid. The yellow reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo, and the resultant yellow oil was purified by flash column chromatography (from 2:3 ethyl acetate/hexane to 5:1 ethyl acetate/methanol) to give bis-THF methylenedioxybenzenesulfonamide 2-picolytethered product (53) (0.0013 g, 30%) as a pale yellow oil: $R_f = 0.35$ (5:1 ethyl acetate/methanol); ^1H NMR (CDCl_3) 8.62-8.57 (1H, m), 7.75-7.70 (1H, m), 7.55-7.48 (1H, m), 7.34 (1H, dd, $J = 8.1, 1.8$ Hz), 7.28-7.20 (1H, obscured m), 7.17-7.10 (3H, m), 6.93-6.87 (3H, m), 6.08 (2H, s), 5.65 (1H, d, $J = 5.0$ Hz), 5.17 (2H, br. s), 5.07-5.01 (1H, m), 4.95-4.89 (1H, m), 4.01-3.93 (1H, m), 3.89-3.80 (3H, m), 3.76-3.67 (1H, m), 3.62-3.58 (1H, m), 3.18-3.09 (1H, m), 3.04-2.87 (4H, m), 2.83-2.73 (2H, m), 1.88-1.79 (1H, m), 1.70-1.47 (2H, obscured m), 0.93 (3H, d, $J = 6.3$ Hz), 0.89 (3H, d, $J = 6.3$ Hz), OH signal not observed; coupled LCMS showed the product as a single major peak with m/z 684 $[\text{M}+\text{H}]^+$; integrated LCMS (205 nm) showed the material as a single major peak at R_t of 2.15 min. (purity = 93%).

25

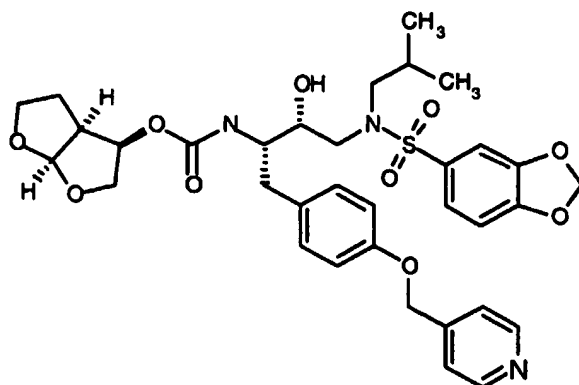
Example 34

**Bis-THF methylenedioxybenzenesulfonamide 3-picolyl
tethered product (52)**

Boc methylenedioxybenzenesulfonamide 3-picolyl tethered
5 product (0.004 g, 0.006 mmol) was dissolved in DCM (0.6
mL). Trifluoroacetic acid (0.3 mL) was added dropwise,
and the reaction was stirred at room temperature for 45
minutes. The solvent was removed in vacuo, and the
resultant orange oil was dissolved in DCM (1 mL).
10 Diisopropylethylamine (0.030 mL, 0.19 mmol) was added
dropwise with stirring at room temperature, followed by
(3R, 3aS, 6aR) hexahydrofuro[2,3-b]furan-2-yl 4-
nitrophenyl carbonate (0.003 g, 0.009 mmol) in one
portion as a solid. The yellow reaction mixture was
15 stirred at room temperature overnight. The solvent was
removed in vacuo, and the resultant yellow oil was
purified by flash column chromatography (2:3 ethyl
acetate/hexane) to give bis-THF
methylenedioxybenzenesulfonamide 3-picolyl tethered
20 product (52) as a pale yellow oil (0.0012 g; an
inseparable mixture with alkylated oxazolidinone): R_f =
0.20 (ethyl acetate); ^1H NMR (CDCl_3) 8.68 (1H, br. s),
8.63-8.56 (1H, m), 7.81-7.74 (1H, m), 7.39-7.30 (1H,
obscured m), 7.34 (1H, dd, J = 8.2, 1.8 Hz), 7.22-7.12
25 (3H, m), 6.94-6.85 (1H, obscured m), 6.90 (2H, d, J = 8.6
Hz), 6.09 (2H, s), 5.67 (1H, d, J = 5.5 Hz), 5.05 (2H,
br. s), 4.95 (1H, d, J = 8.6 Hz), 4.03-3.92 (1H, m),
3.91-3.79 (3H, m), 3.76-3.67 (2H, m), 3.67-3.63 (1H, m),
3.24-3.07 (2H, m), 3.05-2.85 (4H, m), 2.84-2.76 (1H, m),
30 1.91-1.78 (1H, m), 1.77-1.46 (2H, obscured m) 0.91-0.85
(6H, m), OH signal not observed; coupled LCMS showed the
products (alkylated bis-THF derivative/alkylated
oxazolidinone) as a single major peak with m/z 684 $[\text{M}+\text{H}]^+$;

-110-

integrated LCMS (204.5 nm) showed the materials (alkylated *bis*-THF derivative/alkylated oxazolidinone) as a single major peak at R_T of 2.03 min. (combined purity = 80%; desired material and alkylated oxazolidinone).

Example 35

***Bis-THF methylenedioxybenzenesulfonamide 4-picolyt
tethered product (54)***

5

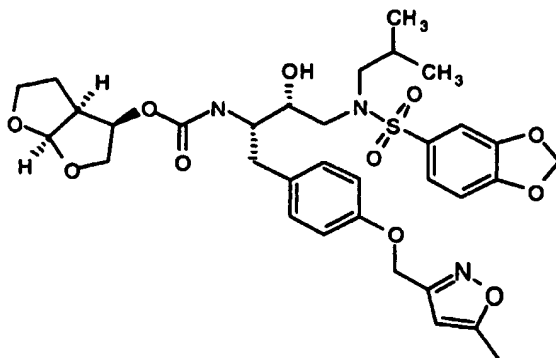
Boc methylenedioxybenzenesulfonamide 4-picolyt tethered product (0.004 g, 0.006 mmol) was dissolved in DCM (0.3 mL). Trifluoroacetic acid (0.1 mL) was added dropwise, and the reaction was stirred at room temperature for 45 minutes. The solvent was removed *in vacuo*, and the resultant orange oil was dissolved in DCM (1 mL). Diisopropylethylamine (0.030 mL, 0.19 mmol) was added dropwise with stirring at room temperature, followed by (3R, 3aS, 6aR) hexahydrofuro[2,3-b]furan-2-yl 4-nitrophenyl carbonate (0.003 g, 0.009 mmol) in one portion as a solid. The yellow reaction mixture was stirred for 7 hours at room temperature. The solvent was removed *in vacuo*, and the resultant yellow oil was purified by flash column chromatography (2:3 ethyl acetate/hexane to 5:1 ethyl acetate/methanol) to give *bis-THF methylenedioxybenzenesulfonamide 4-picolyt tethered product (54)* as a pale yellow oil (0.0015 g; an inseparable mixture with alkylated oxazolidinone): R_f = 0.40 (5:1 ethyl acetate/methanol); coupled LCMS showed the products (alkylated *bis-THF* derivative/alkylated oxazolidinone) with m/z 684 $[M+H]^+$; HPLC (205 nm) showed

20
25

the materials (alkylated *bis*-THF derivative/alkylated oxazolidinone) as a peak at R_T of 1.97 min. (combined purity = 60%; desired material and alkylated oxazolidinone).

5

Example 36



***Bis*-THF methylenedioxybenzenesulfonamide 3-methyl-5-methylisoxazole tethered product (55)**

10

Boc methylenedioxybenzenesulfonamide 3-methyl-5-methylisoxazole tethered product (0.005 g, 0.008 mmol) was dissolved in DCM (0.3 mL). Trifluoroacetic acid (0.1 mL) was added dropwise, and the reaction was stirred at room temperature for 45 minutes. The solvent was removed in vacuo, and the resultant orange oil was dissolved in DCM (1.5 mL). Diisopropylethylamine (0.040 mL, 0.24 mmol) was added dropwise with stirring at room temperature, followed by (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-2-yl 4-nitrophenyl carbonate (0.004 g, 0.012 mmol) in one portion as a solid. The yellow reaction mixture was stirred for 9 hours at room temperature. The solvent was removed in vacuo, and the resultant yellow oil was purified by flash column chromatography (from ethyl acetate to 5:1 ethyl acetate/methanol) to give *bis*-THF methylenedioxybenzenesulfonamide 3-methyl-5-

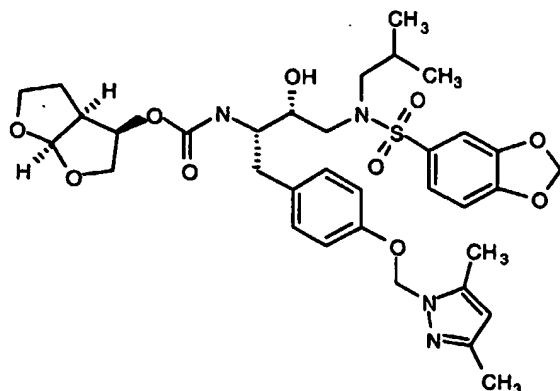
25

- 113 -

methylisoxazole tethered product (55) (0.005 g, 97%) as a pale yellow oil: R_f = 0.50 (5:1 ethyl acetate/methanol); ^1H NMR (CDCl_3) 7.33 (1H, dd, J = 8.2, 1.4 Hz), 7.17-7.10 (3H, m), 6.91-6.86 (3H, m), 6.09 (3H, br. s), 5.65 (1H, d, J = 5.0 Hz), 5.06 (2H, s), 4.94 (1H, d, J = 8.7 Hz), 4.00-3.92 (2H, m), 3.88-3.79 (3H, m), 3.74-3.66 (2H, m), 3.64-3.58 (1H, m), 3.17-3.07 (1H, m), 3.03-2.87 (4H, m), 2.82-2.71 (2H, m), 2.42 (3H, s), 1.86-1.76 (1H, m), 1.70-1.49 (2H, m), 0.93 (3H, d, J = 6.6 Hz), 0.88 (3H, d, J = 6.6 Hz); coupled LCMS showed the product as a single major peak with m/z 688 $[\text{M}+\text{H}]^+$; HPLC (205 nm) showed the material as a single major peak at R_T of 2.38 min. (purity = 82%).

15

Example 37



Bis-THF methylenedioxybenzenesulfonamide 1-methyl-3,5-dimethylpyrazole tethered product (56)

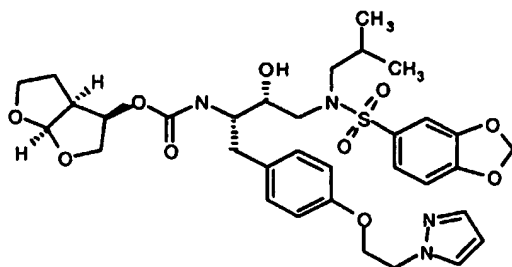
20 Boc methylenedioxybenzenesulfonamide 1-methyl-3,5-
dimethylpyrazole tethered product (0.003 g, 0.005 mmol)
was dissolved in DCM (0.15 mL). Trifluoroacetic acid
(0.05 mL) was added dropwise, and the reaction was
stirred at room temperature for 45 minutes. The solvent
25 was removed *in vacuo*, and the resultant orange oil was
dissolved in DCM (1 mL). Diisopropylethylamine (0.030 mL,

-114-

0.18 mmol) was added dropwise with stirring at room temperature, followed by (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-2-yl 4-nitrophenyl carbonate (0.002 g, 0.007 mmol) in one portion as a solid. The yellow reaction mixture was stirred for 9 hours at room temperature. The solvent was removed in vacuo, and the resultant yellow oil was purified by flash column chromatography (1:1 ethyl acetate/hexane) to give *bis*-THF methylenedioxybenzenesulfonamide 1-methyl-3,5-dimethylpyrazole tethered product (56) (0.001 g, 31%) as a colourless oil: R_f = 0.50 (ethyl acetate); coupled LCMS showed the product as a single major peak with m/z 701 $[M+H]^+$; integrated LCMS (204.5 nm) showed the material as a single major peak at R_T of 1.52 min. (purity = 91%).

15

Example 38

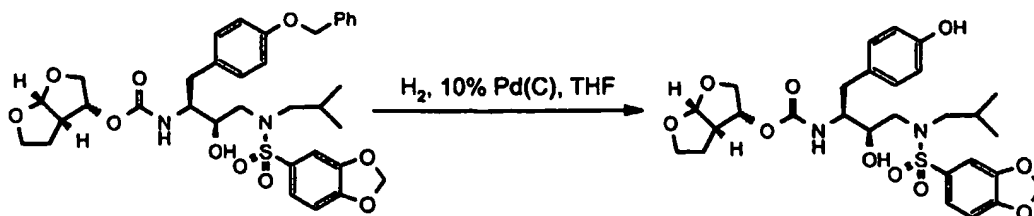


20 ***Bis*-THF methylenedioxybenzenesulfonamide ethylpyrazole tethered product (57)**

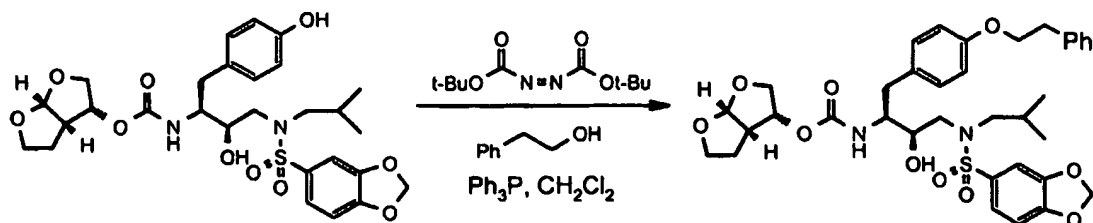
Boc methylenedioxybenzenesulfonamide ethylpyrazole tethered product (0.003 g, 0.005 mmol) was dissolved in DCM (0.15 mL). Trifluoroacetic acid (0.05 mL) was added dropwise, and the reaction was stirred at room temperature for 45 minutes. The solvent was removed in vacuo, and the resultant orange oil was dissolved in DCM

-115-

(1 mL). Diisopropylethylamine (0.030 mL, 0.18 mmol) was added dropwise with stirring at room temperature, followed by (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-2-yl 4-nitrophenyl carbonate (0.002 g, 0.007 mmol) in one
5 portion as a solid. The yellow reaction mixture was stirred for 9 hours at room temperature. The solvent was removed *in vacuo*, and the resultant yellow oil was purified by flash column chromatography (1:1 ethyl acetate/hexane) to give *bis*-THF
10 methylenedioxybenzenesulfonamide ethylpyrazole tethered product (57) (0.001 g, 31%) as a colourless oil: R_f = 0.30 (ethyl acetate); coupled LCMS showed the product as a single major peak with m/z 687 $[M+H]^+$; integrated LCMS (204.5 nm) showed the material as a single major peak at
15 R_T of 1.49 min. (purity = 94%).

Example 39

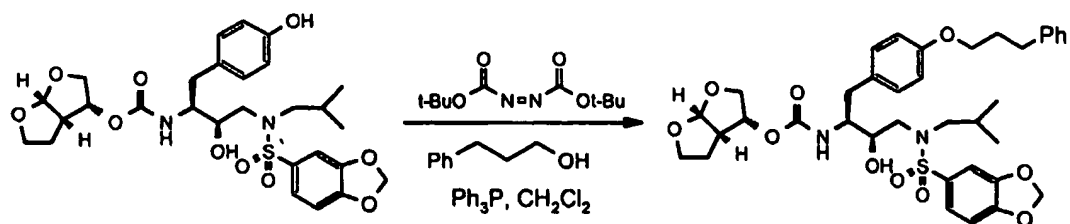
- (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 5 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-(4-hydroxybenzyl)propylcarbamate (201)
 A solution of 8.00 g (11.7 mmol) of (3R,3aS,6aR)-
 hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-
 benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-
 10 (benzyloxy)benzyl]-2-hydroxypropylcarbamate in 200 mL of
 THF was subjected to hydrogenation at 50 psi in the
 presence of 8.0 g of 10% palladium on carbon (Degussa
 type). After 18 hours the reaction vessel was purged
 with nitrogen, catalyst removed by filtration through
 15 celite, and the filtrate concentrated at reduced pressure
 to a volume of 30 mL. The solution was rapidly stirred
 with addition of 30 mL of EtOAc followed by 250 mL of
 hexane. A white suspension resulted which was stirred at
 RT for 1 hour. The solid was collected by vacuum
 20 filtration and dried in vacuo to afford 6.83 g (98%) of
 the desired compound as a white powder. ¹H NMR (DMSO-d₆):
 9.00 (s, 1H), 7.25 (d, 1H), 7.17 (s, 1H), 7.12 (d, 1H),
 7.01 (d, 1H), 6.92 (d, 2H), 6.52 (d, 2H), 6.12 (s, 2H),
 5.46 (d, 1H), 4.93 (d, 1H), 4.80 (q, 1H), 3.80 (dd, 1H),
 25 3.70 (t, 1H), 3.52 (m, 3H), 3.40 (m, 1H), 3.25 (m, 1H),
 3.01-2.62 (m, 5H), 2.28 (t, 1H), 1.89 (m, 1H), 1.38 (m,
 1H), 1.22 (m, 1H), 0.80 (d, 3H), 0.72 (d, 3H). MS(ESI):
 593 (M+H).

Example 40

- (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 5 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(phenethyloxy)benzyl]propylcarbamate (202)
 To a solution of 66 mg (0.25 mmol) of triphenylphosphine
 and 30 μ L (0.25 mmol) of phenethyl alcohol in 3 mL of
 anhydrous CH_2Cl_2 was added 58 mg (0.25 mmol) of di-tert-
 10 butyl azodicarboxylate. The resulting solution was
 stirred at RT for 5 minutes and was then treated with a
 solution of 50 mg (0.084 mmol) of
 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 15 hydroxy-1-(4-hydroxybenzyl)propylcarbamate in 2 mL of
 CH_2Cl_2 . After stirring at RT for 1.5 hours the solution
 was concentrated to dryness and the residue purified by
 flash chromatography (SiO_2 , 4:6 hexane/EtOAc) to give the
 desired product as a white foam in 72% yield. ^1H NMR
 20 (CDCl_3): 7.34-7.17 (m, 6H), 7.15 (s, 1H), 7.07 (d, 2H),
 6.86 (d, 1H), 6.78 (d, 2H), 6.03 (s, 2H), 5.61 (d, 1H),
 4.98 (m, 1H), 4.86 (d, 1H), 4.09 (t, 2H), 3.92 (m, 1H),
 3.84-3.56 (m, 6H), 3.17-3.01 (m, 3H), 3.00-2.81 (m, 4H),
 2.80-2.64 (m, 2H), 1.78 (m, 1H), 1.56 (m, 1H), 1.47 (m,
 25 1H), 0.91 (d, 3H), 0.85 (d, 3H). MS(ESI): 697(M+H).

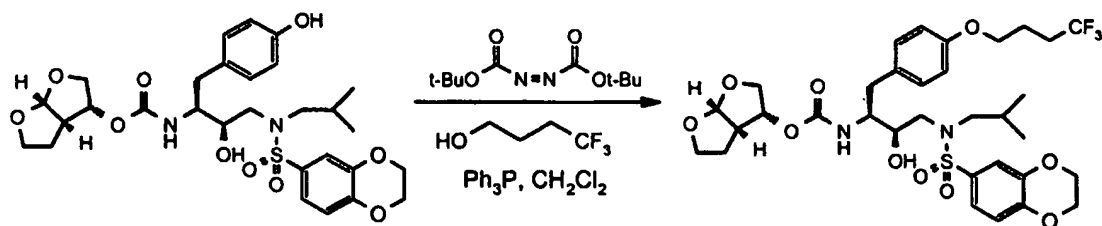
Example 41

-118-



(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 5 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-([3-phenylpropyl]oxy)benzyl]propylcarbamate
 (203)

The title compound was prepared according to example 202
 with the exception that 3-phenyl-1-propanol was used
 10 instead of phenethyl alcohol. ¹H NMR (CDCl₃): 7.33-7.11
 (m, 7H), 7.07 (d, 2H), 6.86 (d, 1H), 6.76 (d, 2H), 6.04
 (s, 2H), 5.61 (d, 1H), 4.99 (q, 1H), 4.86 (d, 1H), 3.97-
 3.72 (m, 7H), 3.65 (m, 2H), 3.09 (dd, 1H), 3.01-2.81 (m,
 4H), 2.80-2.64 (m, 4H), 2.06 (m, 2H), 1.85-1.40 (m, 3H),
 15 0.91 (d, 3H), 0.84 (d, 3H). MS(ESI): 711(M+H).

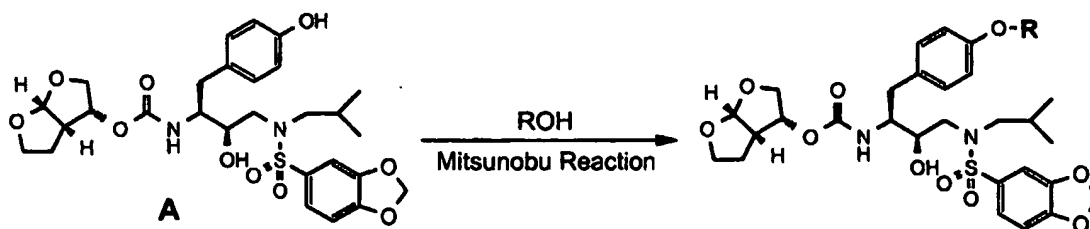
Example 42

20 (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(2,3-dihydro-1,4-benzodioxin-6-
 ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-[4-(4,4,4-
 trifluorobutoxy)benzyl]propylcarbamate (204)

The title compound was prepared according to example 202
 25 with the exception that 4,4,4-trifluorobutanol was used
 instead of phenethyl alcohol. ¹H NMR (CDCl₃): 7.28-7.16

-119-

(m, 2H), 7.08 (d, 2H), 6.91 (d, 1H), 6.75 (d, 2H), 5.61 (d, 1H), 5.04-4.85 (m, 2H), 4.25 (m, 4H), 3.91 (m, 3H), 3.88-3.51 (m, 9H), 3.07 (m, 1H), 3.10-2.82 (m, 4H), 2.81-2.65 (m, 2H), 2.26 (m, 2H), 2.00 (m, 2H), 1.84-1.43 (m, 3H), 0.90 (d, 3H), 0.82 (d, 3H). MS(ESI): 717 (M+H).

Example 43

10

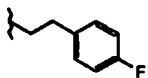
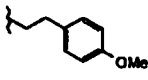
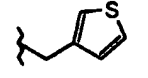
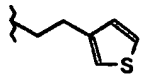
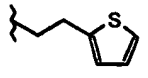
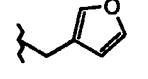
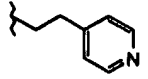
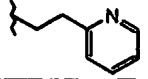
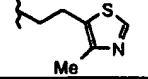
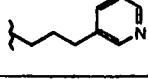
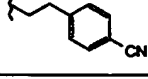
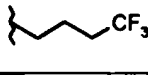
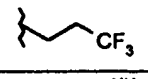
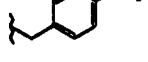
General Procedure for Mitsunobu Alkylations of phenol scaffold A with various alcohols (205-218):

A solution of 2-5 equivalents each of triphenylphosphine and the appropriate alcohol in anhydrous dichloromethane (typically at a concentration of 0.05 M) was treated with di-*t*-butyl azodicarboxylate (2-5 equivalents). Polymer supported triphenylphosphine (Aldrich Chemical) was employed for examples 15-18 to facilitate removal of the triphenylphosphine oxide by-product. After stirring at RT for 5 minutes the solution was treated with 1 equivalent of solid (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-hydroxybenzyl)propylcarbamate and stirring at RT was continued. When the reaction was determined to be complete by thin layer chromatography (2-18 hours) the solution was concentrated in vacuo and the residue purified by flash chromatography (silica gel,

hexane/EtOAc or dichloromethane/2M NH₃ in MeOH) to afford the desired product.

Mass Spectral Data for Compounds 205-218:

5

Example	R	MS (ESI)
205		715 (M+H)
206		727 (M+H)
207		689 (M+H)
208		703 (M+H)
209		703 (M+H)
210		673 (M+H)
211		698 (M+H)
212		698 (M+H)
213		718 (M+H)
214		712 (M+H)
215		722 (M+H)
216		703 (M+H)
217		689 (M+H)
218		698 (M+H)

Proton NMR data for selected compounds from the above table:

5

Example (Compound 209) ^1H NMR(CDCl_3): 7.28 (d, 1H), 7.17-7.04 (m, 4H), 6.95-6.76 (m, 5H), 6.03 (s, 2H), 5.61 (d, 1H), 5.00 (q, 1H), 4.85 (d, 1H), 4.10 (t, 2H), 3.92 (dd, 1H), 3.79 (m, 3H), 3.71-3.48 (m, 3H), 3.24 (t, 2H), 3.10 (m, 1H), 3.01-2.82 (m, 4H), 2.72 (m, 2H), 1.78 (m, 1H), 1.65-1.42 (m, 2H), 0.90 (d, 3H), 0.84 (d, 3H).

Example (Compound 211) ^1H NMR(CDCl_3): 8.53 (br s, 2H), 7.28 (m, 3H), 7.13 (d, 1H), 7.09 (d, 2H), 6.84 (d, 1H), 6.76 (d, 2H), 6.03 (s, 2H), 5.61 (d, 1H), 5.01-4.85 (m, 2H), 4.15 (t, 2H), 3.92 (dd, 1H), 3.85-3.55 (m, 6H), 3.08 (m, 3H), 3.01-2.81 (m, 4H), 2.72 (m, 2H), 1.79 (m, 1H), 1.64-1.41 (m, 2H), 0.89 (d, 3H), 0.82 (d, 3H).

Example (Compound 213) ^1H NMR(CDCl_3): 8.60 (s, 1H), 7.29 (d, 1H), 7.12 (s, 1H), 7.09 (s, 2H), 6.83 (d, 1H), 6.78 (d, 2H), 6.03 (s, 2H), 5.61 (d, 1H), 4.99 (q, 1H), 4.89 (d, 1H), 4.05 (t, 2H), 3.92 (dd, 1H), 3.78 (m, 3H), 3.63 (m, 3H), 3.20 (t, 2H), 3.08 (m, 1H), 3.01-2.81 (m, 4H), 2.72 (m, 2H), 2.41 (s, 3H), 1.78 (m, 1H), 1.58 (m, 1H), 1.46 (m, 1H), 0.89 (s, 3H), 0.82 (s, 3H).

Example (Compound 214) ^1H NMR(CDCl_3): 8.42 (br s, 2H), 7.56 (d, 1H), 7.34-7.19 (m, 2H), 7.13 (s, 1H), 7.07 (d, 2H), 6.85 (d, 1H), 6.73 (d, 2H), 6.03 (s, 2H), 5.60 (d, 1H), 5.10-4.89 (m, 2H), 3.98-3.58 (m, 9H), 3.14-2.65 (m, 9H), 2.08 (m, 2H), 1.80 (m, 1H), 1.61 (m, 1H), 1.50 (m, 1H), 0.89 (d, 3H), 0.81 (d, 3H).

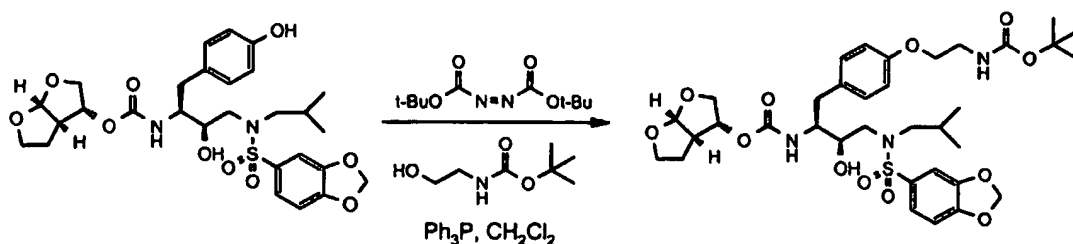
-122-

Example (Compound 215) ^1H NMR(CDCl_3): 7.56 (d, 2H), 7.35 (d, 2H), 7.27 (d, 1H), 7.14 (s, 1H), 7.07 (d, 2H), 6.83 (d, 1H), 6.73 (d, 2H), 6.02 (s, 2H), 5.61 (d, 1H), 4.98 (q, 1H), 4.89 (d, 1H), 4.12 (t, 2H), 3.97-3.58 (m, 7H), 3.08 (m, 3H), 3.01-2.81 (m, 4H), 2.81-2.63 (m, 2H), 1.79 (m, 1H), 1.62-1.38 (m, 2H), 0.89 (d, 3H), 0.83 (d, 3H).

Example (Compound 216) ^1H NMR(CDCl_3): 7.38 (d, 1H), 7.21 (s, 1H), 7.17 (d, 2H), 6.94 (d, 1H), 6.84 (d, 2H), 6.12 (s, 2H), 5.69 (d, 1H), 5.13-4.92 (m, 2H), 4.01 (m, 3H), 3.88 (m, 3H), 3.74 (m, 3H), 3.16 (m, 1H), 3.10-2.89 (m, 4H), 2.81 (m, 2H), 2.43-2.20 (m, 2H), 2.08 (m, 2H), 1.94-1.50 (m, 3H), 0.98 (d, 3H), 0.92 (d, 3H).

15

Example (Compound 217) ^1H NMR(CDCl_3): 7.29 (d, 1H), 7.12 (m, 3H), 6.84 (d, 1H), 6.79 (d, 2H), 6.04 (s, 2H), 5.62 (d, 1H), 5.00 (q, 1H), 4.89 (d, 1H), 4.12 (t, 2H), 3.92 (dd, 1H), 3.80 (m, 2H), 3.66 (m, 2H), 3.12 (dd, 1H), 3.01-2.83 (m, 4H), 2.75 (m, 2H), 2.56 (m, 2H), 1.83-1.44 (m, 5H), 0.91 (d, 3H), 0.83 (d, 3H).

Example 44

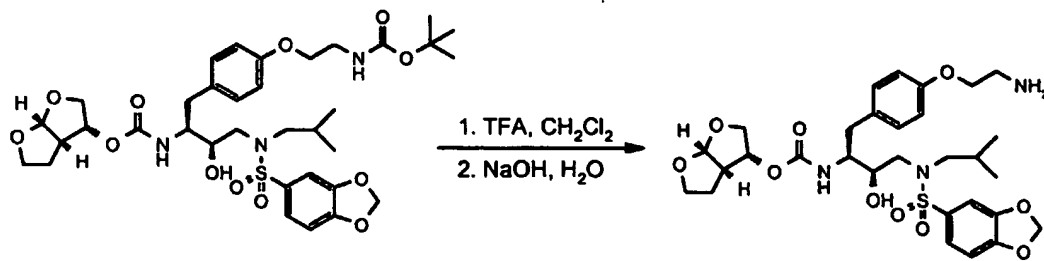
25

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-(4-{2-[(tert-butoxycarbonyl)amino]ethoxy}benzyl)-2-hydroxypropylcarbamate (219)

-123-

The title compound was prepared according to example 202 with the exception that *tert*-butyl 2-hydroxyethylcarbamate was used instead of phenethyl alcohol. ^1H NMR (CDCl_3): 7.30 (dd, 1H), 7.10 (m, 3H), 6.86 (d, 1H), 6.77 (d, 2H), 6.04 (s, 2H), 5.61 (d, 1H), 5.03-4.82 (m, 3H), 3.92 (m, 3H), 3.80 (m, 3H), 3.68 (m, 2H), 3.57 (s, 1H), 3.48 (m, 2H), 3.08 (dd, 1H), 2.92 (m, 4H), 2.75 (m, 2H), 1.78 (m, 1H), 1.64 (m, 1H), 1.41 (m, 10H), 0.90 (d, 3H), 0.83 (d, 3H). MS(ESI): 736(M+H).

10

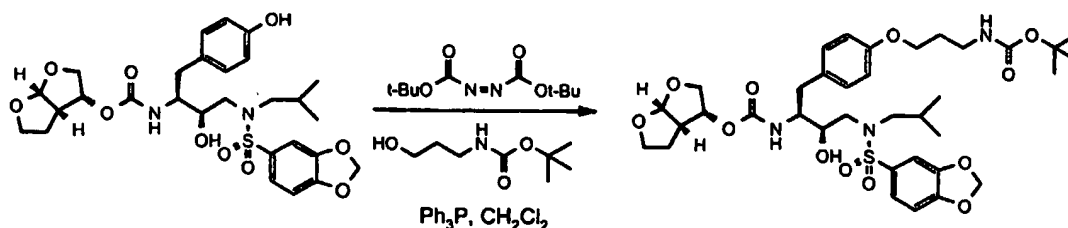
Example 45

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-[4-(2-aminoethoxy)benzyl]-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxypropylcarbamate (220)

A solution of 0.65 g (0.89 mmol) of (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-(4-{2-[(*tert*-butoxycarbonyl)amino]ethoxy}benzyl)-2-hydroxypropylcarbamate in 10 mL of anhydrous CH_2Cl_2 was treated with 15 mL of TFA and the resulting solution was stirred at RT. After 2 hours the solution was evaporated at reduced pressure and the residue redissolved in CH_2Cl_2 . The solution was washed with 0.5 M aqueous NaOH (1x), water (2x), dried over MgSO_4 , and concentrated *in vacuo*. The crude product was purified by flash chromatography (SiO_2 , 95:5 CH_2Cl_2 /2M NH_3 in MeOH) to afford 0.40 g (70%)

-124-

of the desired compound as a white foam. ^1H NMR (CDCl_3):
 7.39 (dd, 1H), 7.12 (s, 1H), 7.08 (d, 2H), 6.84 (d, 1H),
 6.77 (d, 2H), 6.03 (s, 2H), 5.61 (d, 1H), 4.95 (m, 2H),
 4.00-3.60 (m, 8H), 3.16-2.62 (m, 10H), 2.20-1.40 (m, 5H),
 0.90 (d, 3H), 0.82 (d, 3H). MS(ESI): 636(M+H).

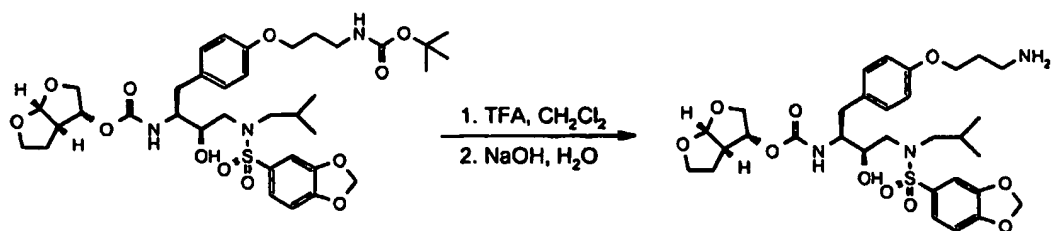
Example 46

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-(4-{3-
 [(tert-butoxycarbonyl)amino]propoxy}benzyl)-2-
 hydroxypropylcarbamate (221)

The title compound was prepared according to example 202
 with the exception that tert-butyl 3-
 hydroxypropylcarbamate was used instead of phenethyl
 alcohol. ^1H NMR (CDCl_3): 7.30 (d, 1H), 7.13 (s, 1H), 7.08
 (d, 2H), 6.84 (d, 1H), 6.76 (d, 2H), 6.06 (s, 2H), 5.61
 (d, 1H), 5.00 (q, 1H), 4.88 (d, 1H), 4.70 (br s, 1H),
 3.93 (m, 3H), 3.80 (m, 4H), 3.67 (m, 2H), 3.26 (m, 2H),
 3.09 (dd, 1H), 2.92 (m, 4H), 2.72 (m, 2H), 1.91 (m, 2H),
 1.79 (m, 1H), 1.62 (m, 1H), 1.51 (m, 1H), 1.40 (s, 9H),
 0.90 (d, 3H), 0.83 (d, 3H). MS(ESI): 750(M+H).

Example 47

-125-



(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-[4-(3-aminopropoxy)benzyl]-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxypropylcarbamate (222)

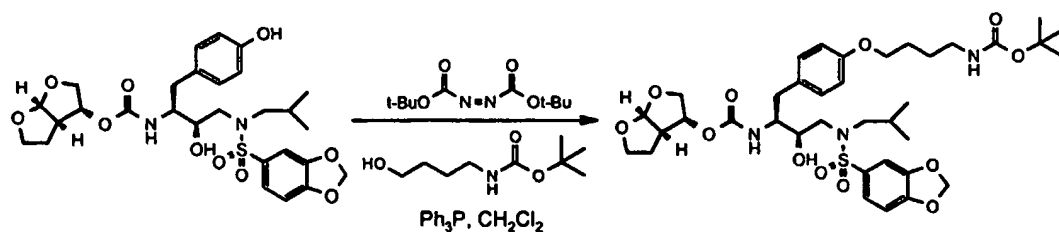
The title compound was prepared according to example 202.

¹H NMR (CDCl₃): 7.29 (d, 1H), 7.15 (s, 1H), 7.09 (d, 2H), 6.85 (d, 1H), 6.78 (d, 2H), 6.04 (s, 2H), 5.61 (d, 1H), 5.00 (m, 2H), 4.03-3.87 (m, 4H), 3.80 (m, 3H), 3.66 (m, 2H), 3.14-2.40 (m, 11H), 1.94 (m, 2H), 1.80 (m, 1H), 1.62 (m, 1H), 1.49 (m, 1H), 0.90 (d, 3H), 0.82 (d, 3H).

MS (ESI): 650 (M+H).

15

Example 48



(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-(4-{4-[(tert-butoxycarbonyl)amino]butoxy}benzyl)-2-hydroxypropylcarbamate (223)

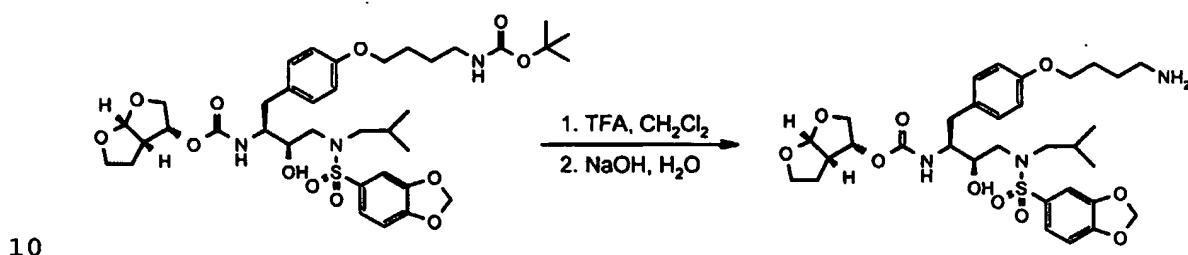
The title compound was prepared according to example 202

with the exception that tert-butyl 3-

hydroxybutylcarbamate (prepared by reaction of 4-amino-1-

-126-

butanol with di-tert-butyl-dicarbonate in CH_2Cl_2) was used instead of phenethyl alcohol. ^1H NMR (CDCl_3): 7.37 (d, 1H), 7.21 (s, 1H), 7.14 (d, 2H), 6.93 (d, 1H), 6.84 (d, 2H), 6.13 (s, 2H), 5.69 (d, 1H), 5.08 (q, 1H), 4.95 (d, 1H), 4.63 (br s, 1H), 4.08-3.63 (m, 9H), 3.30-2.72 (m, 9H), 1.96-1.40 (m, 16H), 0.97 (d, 3H), 0.90 (d, 3H). MS (ESI): 764 (M+H).

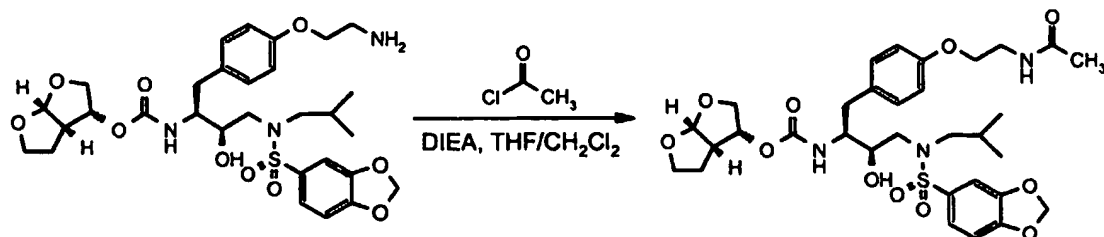
Example 49

10

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-[4-(4-aminobutoxy)benzyl]-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxypropylcarbamate (224)

The title compound was prepared according to example 202. ^1H NMR (CDCl_3): 7.30 (d, 1H), 7.13 (s, 1H), 7.06 (d, 2H), 6.85 (d, 1H), 6.75 (d, 2H), 6.04 (s, 2H), 5.60 (d, 1H), 5.00 (m, 2H), 3.97-3.71 (m, 7H), 3.66 (m, 2H), 3.22-2.60 (m, 11H), 1.87-1.53 (m, 6H), 1.43 (m, 1H), 0.88 (d, 3H), 0.82 (d, 3H). MS (ESI): 664 (M+H).

20

Example 50

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-[4-

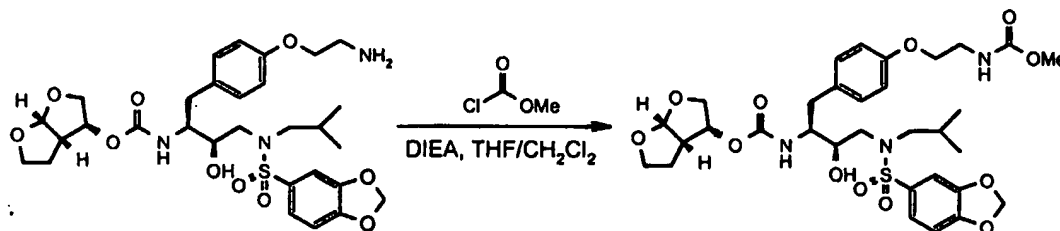
25

-127-

[2-(acetylamino)ethoxy]benzyl}-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxypropylcarbamate (225)

A solution of 21 mg (0.033 mmol) of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-[4-(2-aminoethoxy)benzyl]-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxypropylcarbamate in 2 mL of 1:1 THF/CH₂Cl₂ was treated with 9 µL (0.050 mmol) of *N,N*-diisopropylethylamine followed by 2.6 µL (0.036 mmol) of acetyl chloride. The resulting solution was stirred at RT. After 1.5 hours the solution was concentrated in vacuo and the residue subjected to flash chromatography (SiO₂, 95:5 CH₂Cl₂/MeOH) to afford the desired compound in 86 % yield as a white foam. ¹H NMR (CDCl₃): 7.29 (dd, 1H), 7.16-7.04 (m, 3H), 7.05 (d, 1H), 6.76 (d, 2H), 6.05 (s, 2H), 5.91 (br s, 1H), 5.01 (d, 1H), 5.05-4.89 (m, 2H), 3.94 (m, 3H), 3.80 (m, 3H), 3.72-3.51 (m, 5H), 3.08 (dd, 1H), 3.01-2.83 (m, 4H), 2.74 (m, 2H), 1.97 (s, 3H), 1.86-1.45 (m, 3H), 0.90 (d, 3H), 0.84 (d, 3H). MS(ESI): 678 (M+H).

Example 51



25

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-

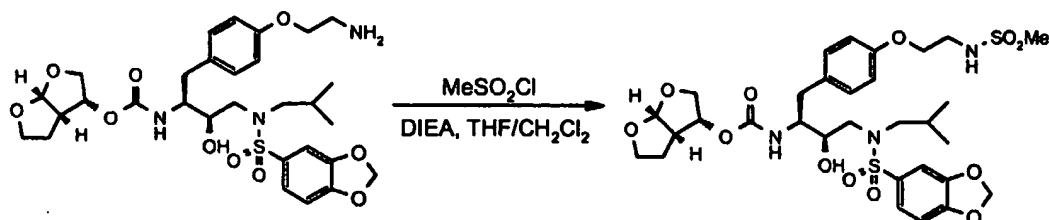
hydroxy-1-(4-{2-[(methoxycarbonyl)amino]ethoxy}
benzyl)propylcarbamate (226)

The title compound was prepared according to example 225
with the exception that methyl chloroformate was used

5 instead of acetyl chloride. ^1H NMR (CDCl_3): 7.29 (dd, 1H),
7.16-7.02 (m, 3H), 6.84 (d, 1H), 6.76 (d, 2H), 6.04 (s,
2H), 5.61 (d, 1H), 5.18-4.84 (m, 3H), 4.02-3.43 (m, 14H),
3.09 (m, 1H), 2.91 (m, 4H), 2.72 (m, 2H), 1.85-1.43 (m,
3H), 0.89 (d, 3H), 0.92 (d, 3H). MS(ESI): 694 (M+H).

10

Example 52



15

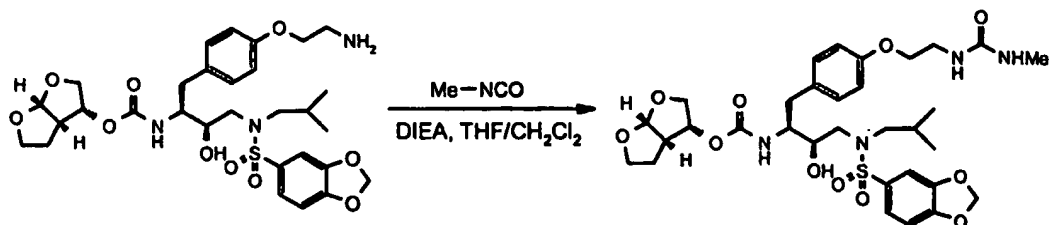
(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
hydroxy-1-(4-{2-[(methanesulfonyl)amino]ethoxy}

20 benzyl)propylcarbamate (227)

The title compound was prepared according to example 225
with the exception that methanesulfonyl chloride was used

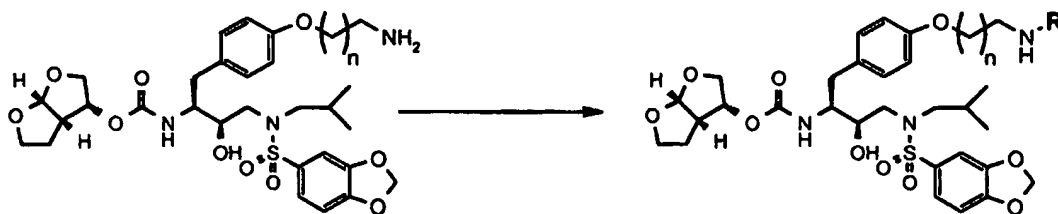
instead of acetyl chloride. ^1H NMR (CDCl_3): 7.29 (dd, 1H),
7.11 (m, 3H), 6.86 (d, 1H), 6.77 (d, 2H), 6.04 (s, 2H),
25 5.61 (d, 1H), 4.98 (m, 2H), 4.84 (m, 1H), 4.09-3.44 (m,
11H), 3.12-2.82 (m, 8H), 2.74 (m, 2H), 1.88-1.43 (m, 3H),
0.89 (d, 3H), 0.81 (d, 3H). MS(ESI): 714 (M+H).

-129-

Example 53

5 (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(2-{[(methylamino)carbonyl]amino}
 ethoxy)benzyl]propylcarbamate (228)

The title compound was prepared according to example 225
 10 with the exception that methyl isocyanate was used
 instead of acetyl chloride. ¹H NMR (CDCl₃): 7.29 (dd, 1H),
 7.13 (s, 1H), 7.08 (d, 2H), 6.84 (d, 1H), 6.76 (d, 2H),
 6.05 (s, 2H), 5.61 (d, 1H), 5.10-4.90 (m, 2H), 4.04-3.48
 (m, 11H), 3.15-2.67 (m, 10H), 1.80 (m, 1H), 1.62 (m, 1H),
 15 1.47 (m, 1H), 0.85 (m, 6H). MS(ESI): 693(M+H).

Example 54

20

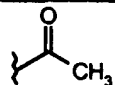
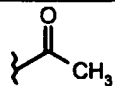
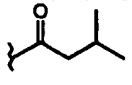
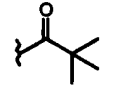
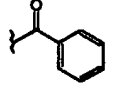
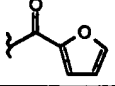
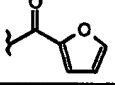
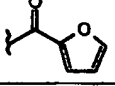
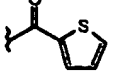
*General procedure for reactions of primary amine
 scaffolds with various electrophiles (229-260):* A
 solution of the primary amine (0.02 M) in anhydrous CH₂Cl₂
 at 0°C was treated with 1.5 equivalents of N,N-
 25 diisopropylethylamine (omitted for reactions with

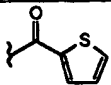
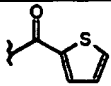
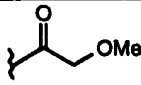
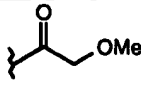
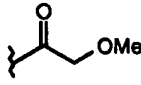
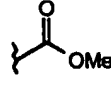
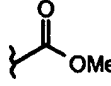
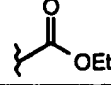
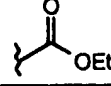
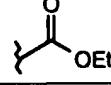
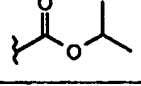
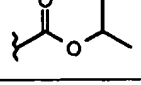
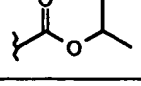
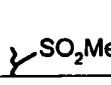
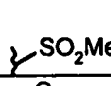
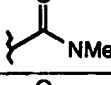
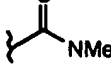
isocyanates and isothiocyanates, examples 56-60) followed by 1.05 equivalent of the appropriate electrophile (acid chloride, chloroformate, sulfonyl chloride, carbamyl chloride, isocyanate, isothiocyanate). The resulting

5 solution was allowed to warm to RT with stirring. When analysis by TLC indicated the reaction to be complete (2-18 hours) the solution was concentrated *in vacuo* and the residue subjected to flash chromatography (SiO₂, CH₂Cl₂/MeOH or hexane/EtOAc) to afford the desired

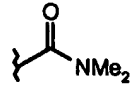
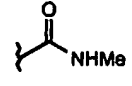
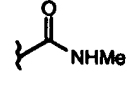
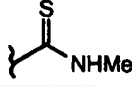
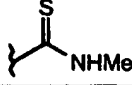
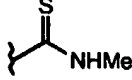
10 product.

Mass Spectral Data for Compounds 29-60:

Example	n	R	MS (ESI)
229	2		692 (M+H)
230	3		706 (M+H)
231	2		734 (M+H)
232	2		734 (M+H)
233	2		754 (M+H)
234	1		730 (M+H)
235	2		744 (M+H)
236	3		758 (M+H)
237	1		746 (M+H)

238	2		760 (M+H)
239	3		774 (M+H)
240	1		708 (M+H)
241	2		722 (M+H)
242	3		736 (M+H)
243	2		708 (M+H)
244	3		722 (M+H)
245	1		708 (M+H)
246	2		722 (M+H)
247	3		736 (M+H)
248	1		722 (M+H)
249	2		736 (M+H)
250	3		750 (M+H)
251	2		728 (M+H)
252	3		742 (M+H)
253	1		707 (M+H)
254	2		721 (M+H)

-132-

255	3		735 (M+H)
256	2		707 (M+H)
257	3		721 (M+H)
258	1		709 (M+H)
259	2		723 (M+H)
260	3		737 (M+H)

Proton NMR data for selected compounds from the above table:

5

Example (Compound 231) NMR(CDCl₃): 7.29 (d, 1H), 7.13 (s, 1H), 7.08 (d, 2H), 6.86 (d, 1H), 6.75 (d, 2H), 6.04 (s, 2H), 5.80 (br s, 1H), 5.60 (d, 1H), 4.98 (m, 2H), 3.92 (m, 3H), 3.79 (m, 3H), 3.65 (m, 2H), 3.40 (q, 2H), 3.15-
 10 2.65 (m, 8H), 2.13-1.90 (m, 5H), 1.80 (m, 1H), 1.62 (m, 1H), 1.49 (m, 1H), 0.95-0.78 (m, 12H).

Example (Compound 233) NMR(CDCl₃): 7.72 (d, 2H), 7.43 (d, 1H), 7.38 (m, 2H), 7.29 (d, 1H), 7.10 (m, 3H), 6.84 (d, 1H), 6.77 (d, 2H), 6.65 (br s, 1H), 6.03 (s, 2H), 5.59 (d, 1H), 4.98 (m, 2H), 4.02 (t, 2H), 3.91 (dd, 1H), 3.79 (m, 3H), 3.63 (m, 5H), 3.14-2.66 (m, 7H), 2.07 (m, 2H), 1.79 (m, 1H), 1.61 (m, 1H), 1.49 (m, 1H), 0.89 (d, 3H), 0.92 (d, 3H).

20

Example (Compound 235) NMR(CDCl₃): 7.41 (s, 1H), 7.28 (d, 1H), 7.18-7.04 (m, 4H), 6.87 (d, 1H), 6.79 (m, 3H), 6.45

-133-

(m, 1H), 6.04 (s, 2H), 5.60 (d, 1H), 4.96 (m, 2H), 4.02 (t, 2H), 3.91 (dd, 1H), 3.80 (m, 3H), 3.73-3.52 (m, 5H), 3.08 (m, 1H), 3.01-2.82 (m, 4H), 2.74 (m, 2H), 2.05 (m, 2H), 1.80 (m, 1H), 1.63 (m, 1H), 1.50 (m, 1H), 0.90 (d, 3H), 0.82 (d, 3H).

Example (Compound 236) NMR(CDCl₃): 7.38 (s, 1H), 7.29 (d, 1H), 7.13 (s, 1H), 7.07 (m, 3H), 6.84 (d, 1H), 6.77 (d, 2H), 6.46 (m, 2H), 6.03 (s, 2H), 5.60 (d, 1H), 4.96 (m, 2H), 3.92 (m, 3H), 3.80 (m, 3H), 3.66 (m, 3H), 3.47 (q, 2H), 3.08 (dd, 1H), 2.92 (m, 4H), 2.73 (m, 2H), 1.80 (m, 5H), 1.62 (m, 1H), 1.48 (m, 1H), 0.90 (d, 3H), 0.82 (d, 3H).

Example (Compound 237) NMR(CDCl₃): 7.50 (m, 1H), 7.43 (d, 1H), 7.29 (d, 1H), 7.12 (m, 3H), 7.02 (m, 1H), 6.85 (d, 1H), 6.80 (d, 2H), 6.43 (br s, 1H), 6.04 (s, 2H), 5.60 (d, 1H), 4.96 (m, 2H), 4.05 (t, 2H), 3.91 (dd, 1H), 3.80 (m, 6H), 3.66 (m, 2H), 3.08 (dd, 1H), 3.00-2.81 (m, 4H), 2.73 (m, 2H), 1.80 (m, 1H), 1.62 (m, 1H), 1.50 (m, 1H), 0.89 (d, 3H), 0.82 (d, 3H).

Example (Compound 238) NMR(CDCl₃): 7.47 (d, 1H), 7.42 (d, 1H), 7.30 (d, 1H), 7.11 (m, 3H), 7.03 (t, 1H), 6.85 (t, 1H), 6.79 (d, 2H), 6.51 (br s, 1H), 6.04 (s, 2H), 5.61 (d, 1H), 4.98 (m, 2H), 4.02 (t, 2H), 3.91 (dd, 1H), 3.80 (m, 3H), 3.70-3.52 (m, 4H), 3.08 (m, 1H), 3.00-2.83 (m, 5H), 2.81-2.67 (m, 2H), 2.07 (m, 2H), 1.80 (m, 1H), 1.62 (m, 1H), 1.50 (m, 1H), 0.89 (d, 3H), 0.81 (d, 3H).

30

Example (Compound 241) NMR(CDCl₃): 7.29 (d, 1H), 7.12 (s, 1H), 7.08 (d, 2H), 6.89 (br s, 1H), 6.85 (d, 1H), 6.77 (d, 2H), 6.04 (s, 2H), 5.61 (d, 1H), 4.99 (q, 1H), 4.91

-134-

(d, 1H), 4.01-3.89 (m, 3H), 3.88-3.72 (m, 6H), 3.67 (m, 2H), 3.46 (q, 2H), 3.39 (s, 3H), 3.09 (dd, 1H), 3.01-2.82 (m, 4H), 2.81-2.67 (m, 2H), 1.98 (m, 2H), 1.80 (m, 1H), 1.63 (m, 1H), 1.50 (m, 1H), 0.89 (d, 3H), 0.82 (d, 3H).

5

Example (Compound 243) NMR(CDCl₃): 7.38 (d, 1H), 7.20 (s, 1H), 7.16 (d, 2H), 6.92 (d, 1H), 6.85 (d, 2H), 6.12 (s, 2H), 5.69 (d, 1H), 5.14-4.89 (m, 3H), 4.01 (m, 3H), 3.89 (m, 3H), 3.73 (m, 6H), 3.42 (m, 2H), 3.18 (dd, 1H), 3.11-10 2.90 (m, 4H), 2.82 (m, 2H), 2.01 (m, 2H), 1.93-1.52 (m, 3H), 0.98 (d, 3H), 0.92 (d, 3H).

Example (Compound 244) NMR(CDCl₃): 7.38 (d, 1H), 7.22 (s, 1H), 7.14 (d, 2H), 6.93 (d, 1H), 6.85 (d, 2H), 6.13 (s, 15 2H), 5.69 (d, 1H), 5.12-4.90 (m, 2H), 4.82 (br s, 1H), 4.07-3.61 (m, 12H), 3.36-3.10 (m, 3H), 3.09-2.90 (m, 4H), 2.90-2.70 (m, 2H), 1.95-1.62 (m, 6H), 1.56 (m, 1H), 0.98 (d, 3H), 0.91 (d, 3H).

Example (Compound 247) NMR(CDCl₃): 7.29 (d, 1H), 7.13 (s, 1H), 7.07 (d, 2H), 6.84 (d, 1H), 6.76 (d, 2H), 6.06 (s, 2H), 5.61 (d, 1H), 5.02-4.84 (m, 2H), 4.71 (br s, 1H), 4.08 (q, 2H), 3.97-3.73 (m, 7H), 3.65 (m, 2H), 3.20 (m, 2H), 3.08 (dd, 1H), 3.00-2.82 (m, 4H), 2.73 (m, 2H), 1.78 25 (m, 3H), 1.64 (m, 3H), 1.49 (m, 1H), 1.20 (t, 3H), 0.89 (d, 3H), 0.82 (d, 3H).

Example (Compound 249) NMR(CDCl₃): 7.29 (d, 1H), 7.12 (s, 1H), 7.09 (d, 2H), 6.84 (d, 1H), 6.77 (d, 2H), 6.06 (s, 2H), 5.61 (d, 1H), 5.04-4.70 (m, 4H), 3.94 (m, 3H), 3.80 30 (m, 3H), 3.67 (m, 2H), 3.32 (m, 2H), 3.07 (dd, 1H), 2.91 (m, 5H), 2.75 (m, 2H), 1.94 (m, 2H), 1.80 (m, 1H), 1.63

-135-

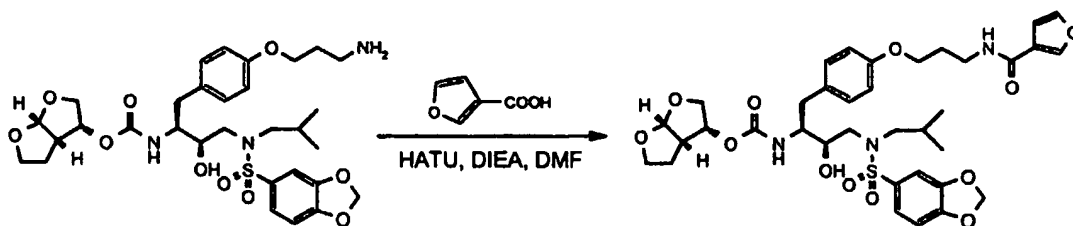
(m, 1H), 1.51 (m, 1H), 1.20 (d, 6H), 0.90 (d, 3H), 0.82 (d, 3H).

Example (Compound 250) NMR(CDCl₃): 7.29 (d, 1H), 7.12 (s, 1H), 7.02 (d, 2H), 6.84 (d, 1H), 6.76 (d, 2H), 6.03 (s, 2H), 5.61 (d, 1H), 5.00 (q, 1H), 4.88 (m, 2H), 4.65 (br s, 1H), 3.90 (m, 3H), 3.80 (m, 3H), 3.66 (m, 2H), 3.20 (m, 2H), 3.10 (dd, 1H), 2.91 (m, 5H), 2.73 (m, 2H), 1.78 (m, 3H), 1.62 (m, 3H), 1.48 (m, 1H), 1.20 (d, 6H), 0.89 (d, 3H), 0.81 (d, 3H).

Example (Compound 252) NMR(CDCl₃): 7.29 (d, 1H), 7.13 (s, 1H), 7.08 (d, 2H), 6.83 (d, 1H), 6.76 (d, 2H), 6.04 (s, 2H), 5.60 (d, 1H), 4.96 (m, 2H), 4.53 (br s, 1H), 3.92 (m, 3H), 3.79 (m, 3H), 3.67 (m, 2H), 3.16 (m, 2H), 3.07 (dd, 1H), 3.04-2.82 (m, 8H), 2.81-2.65 (m, 2H), 1.87-1.54 (m, 6H), 1.49 (m, 1H), 0.89 (d, 3H), 0.82 (d, 3H).

Example (Compound 254) NMR(CDCl₃): 7.29 (d, 1H), 7.12 (s, 1H), 7.08 (d, 2H), 6.85 (d, 1H), 6.74 (d, 2H), 6.04 (s, 2H), 5.60 (d, 1H), 5.00 (m, 2H), 4.82 (br s, 1H), 4.01-3.88 (m, 3H), 3.80 (m, 3H), 3.66 (m, 2H), 3.37 (t, 2H), 3.15-2.82 (m, 12H), 2.81-2.65 (m, 2H), 1.96 (m, 2H), 1.80 (m, 1H), 1.62 (m, 1H), 1.50 (m, 1H), 0.90 (d, 3H), 0.82 (d, 3H).

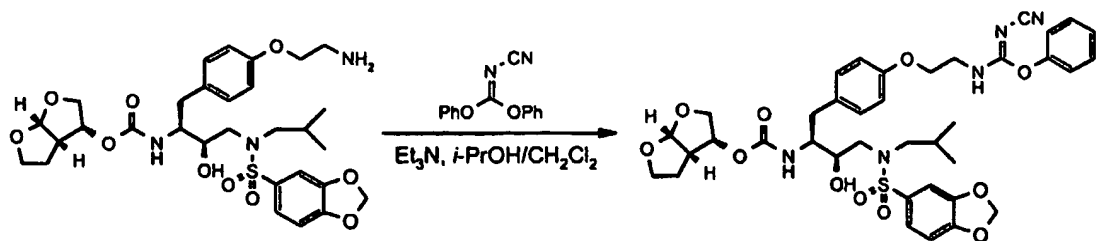
Example (Compound 260) NMR(CDCl₃): 7.29 (d, 1H), 7.13 (s, 1H), 7.07 (d, 2H), 6.86 (d, 1H), 6.75 (d, 2H), 6.04 (s, 2H), 5.60 (d, 1H), 4.98 (m, 2H), 3.90 (m, 3H), 3.80 (m, 3H), 3.65 (m, 2H), 3.48 (br s, 2H), 3.08 (m, 1H), 3.02-2.81 (m, 10H), 2.80-2.62 (m, 2H), 1.80 (m, 5H), 1.61 (m, 1H), 1.48 (m, 1H), 0.88 (d, 3H), 0.81 (d, 3H).

Example 55

5 (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-{4-[3-
 (3-furoylamino)propoxy]benzyl}-2-hydroxypropylcarbamate
 (261)

A solution of 44 mg (0.068 mmol) of (3*R*,3*aS*,6*aR*)-
 10 hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-[4-(3-
 aminopropoxy)benzyl]-3-[(1,3-benzodioxol-5-
 ylsulfonyl)(isobutyl)amino]-2-hydroxypropylcarbamate, 15
 mg (0.14 mmol) of 3-furoic acid, and 36 μ L (0.20 mmol) of
N,N-diisopropylethylamine in 2 mL of anhydrous DMF was
 15 treated with 52 mg (0.14 mmol) of *O*-(7-azabenzotriazol-1-
 yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)
 and the resulting solution was stirred at RT. After 18
 hours the solution was concentrated in vacuo and the
 residue subjected to flash chromatography (SiO₂, 97:3
 20 CH₂Cl₂/MeOH) to afford 38 mg (75%) of the desired compound
 as a white foam. ¹H NMR (CDCl₃): 7.88 (s, 1H), 7.38 (s,
 1H), 7.29 (d, 1H), 7.10 (m, 3H), 6.84 (d, 1H), 6.76 (d,
 2H), 6.56 (s, 1H), 6.34 (br s, 1H), 6.05 (s, 2H), 5.60
 (d, 1H), 5.00 (m, 2H), 4.01 (t, 2H), 3.90 (dd, 1H), 3.80
 25 (m, 3H), 3.64 (m, 2H), 3.55 (q, 2H), 3.17-2.63 (m, 8H),
 2.03 (m, 2H), 1.80 (m, 1H), 1.61 (m, 1H), 1.49 (m, 1H),
 0.89 (d, 3H), 0.83 (d, 3H). MS(ESI): 744 (M+H).

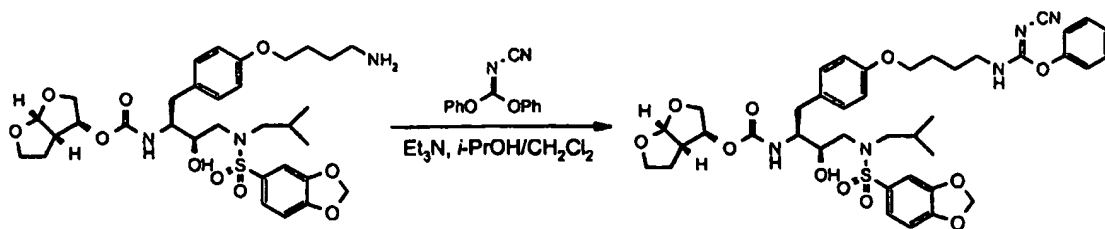
Example 56



(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-(2-
 5 {[(E and/or Z)-(cyanoimino)(phenoxy)methyl]amino}
 ethoxy)benzyl]-2-hydroxypropylcarbamate (262)

A solution of 0.20 g (0.32 mmol) of (3R,3aS,6aR)-
 hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-[4-(2-
 aminoethoxy)benzyl]-3-[(1,3-benzodioxol-5-
 10 ylsulfonyl)(isobutyl)amino]-2-hydroxypropylcarbamate, 83
 mg (0.35 mmol) of diphenyl cyanocarbonimidate, and 66 μ L
 of (0.47 mmol) triethylamine in 12 mL of 1:1 i-PrOH/ CH_2Cl_2
 was stirred at RT. After 2.5 hours the solution was
 concentrated to dryness at reduced pressure and the
 15 residue subjected to flash chromatography (SiO_2 , 95:5
 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford 0.24 g (96%) of the desired
 compound as a white foam. ^1H NMR (CDCl_3): 7.47-7.21 (m,
 4H), 7.20-7.02 (m, 5H), 6.88-6.63 (m, 3H), 6.42 (br s,
 1H), 6.05 (s, 2H), 5.61 (d, 1H), 4.99 (m, 2H), 4.20-3.50
 20 (m, 11H), 3.09 (m, 1H), 3.01-2.82 (m, 4H), 2.76 (m, 2H),
 1.78 (m, 1H), 1.72-1.43 (m, 2H), 0.90 (d, 3H), 0.81 (d,
 3H). MS(ESI): 780 (M+H).

Example 57

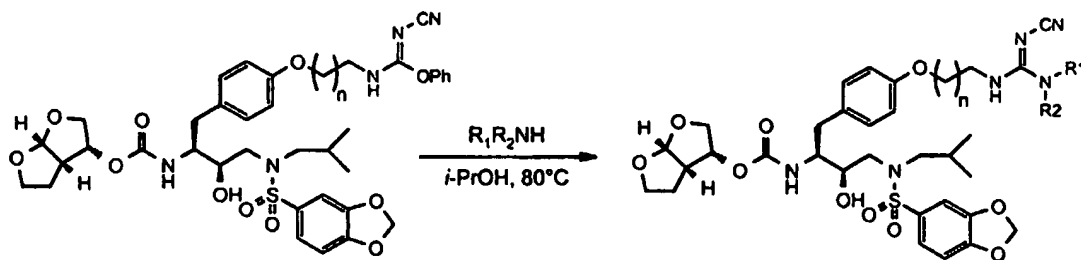


(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-(4-
 5 {[(E and/or Z)-(cyanoimino)(phenoxy)methyl]amino}
 butoxy)benzyl]-2-hydroxypropylcarbamate (263)

According to example 262, (3R,3aS,6aR)-hexahydrofuro[2,3-
 b]furan-3-yl (1S,2R)-1-[4-(4-aminobutoxy)benzyl]-3-[(1,3-
 benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-

10 hydroxypropylcarbamate was converted to the desired
 compound which was obtained in 98% yield as a white foam.
¹H NMR (CDCl₃): 7.52-7.26 (m, 4H), 7.25-7.07 (m, 5H),
 6.97-6.67 (m, 4H), 6.12 (s, 2H), 5.69 (d, 1H), 5.06 (m,
 2H), 4.10-3.40 (m, 11H), 3.22-2.73 (m, 7H), 2.00-1.55 (m,
 15 7H), 0.96 (d, 3H), 0.91 (d, 3H). MS(ESI): 808 (M+H).

Example 58



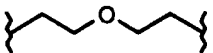
20 General procedure for the synthesis of cyanoguanidines
 from imidocarbamate scaffolds (264-269):

A mixture of 0.05 mmol of imidocarbamate intermediate in
 3 mL of isopropanol in a sealed tube was treated with 10-
 20 equivalents of amine (2M NH₃ in MeOH, 8M MeNH₂ in EtOH,
 25 2M Me₂NH in THF, neat morpholine). Upon heating, the

-139-

solid starting material dissolved to give a clear solution. After stirring at 80°C for 3 hours the solution was cooled to RT and concentrated to dryness at reduced pressure. The residue was subjected to flash
 5 chromatography (SiO₂, CH₂Cl₂/MeOH or CH₂Cl₂/2M NH₃ in MeOH) to afford the desired compound as white foam.

Mass Spectral Data for Compounds 264-269

Example	n	R ₁	R ₂	MS (ESI)
264	1	H	H	703 (M+H)
265	1	Me	H	717 (M+H)
266	1			773 (M+H)
267	3	H	H	731 (M+H)
268	3	Me	H	745 (M+H)
269	3	Me	Me	759 (M+H)

10

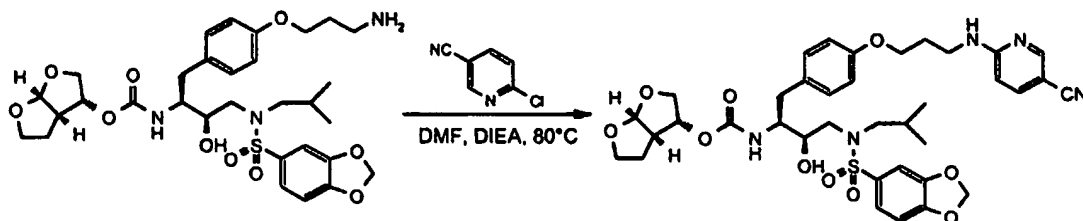
Proton NMR data for selected compounds from the above table:

Example (Compound 265) ¹H NMR(CDCl₃): 7.30 (d, 1H), 7.11 (m, 3H), 6.86 (d, 1H), 6.76 (d, 2H), 6.04 (s, 2H), 5.87 (br s, 1H), 5.65-5.42 (m, 2H), 5.09 (d, 1H), 5.00 (q, 1H), 4.01 (m, 2H), 3.92 (dd, 1H), 3.79 (m, 3H), 3.71-3.52 (m, 5H), 3.11-2.66 (10H), 1.80 (m, 1H), 1.61 (m, 1H), 1.50 (m, 1H), 0.86 (m, 6H).

20

-140-

Example (Compound 269) ^1H NMR(CDCl_3): 7.29 (d, 1H), 7.12 (s, 1H), 7.08 (d, 2H), 6.84 (d, 1H), 6.74 (d, 2H), 6.03 (s, 2H), 5.60 (d, 1H), 5.06-4.87 (m, 3H), 3.91 (m, 3H), 3.79 (m, 3H), 3.64 (m, 3H), 3.49 (q, 2H), 3.15-2.65 (m, 13H), 1.89-1.54 (m, 6H), 1.48 (m, 1H), 0.86 (m, 6H).

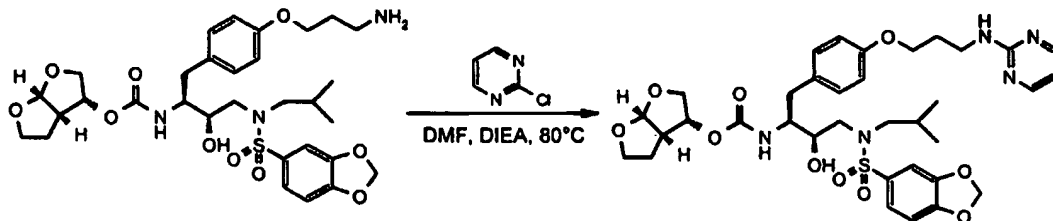
Example 59

- 10 (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-{3-
 [(5-cyano-2-pyridinyl)amino]propoxy}benzyl)-2-
 hydroxypropylcarbamate (270)
- A solution of 35 mg (0.054 mmol) of (3R,3aS,6aR)-
 15 hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-[4-(3-
 aminopropoxy)benzyl]-3-[(1,3-benzodioxol-5-
 ylsulfonyl)(isobutyl)amino]-2-hydroxypropylcarbamate, 22
 mg (0.16 mmol) of 2-chloro-5-cyanopyridine, and 38 μL
 (0.22 mmol) of *N,N*-diisopropylethylamine in 0.5 mL of
 20 anhydrous DMF was heated to 80°C with stirring. After 6
 hours the solution was cooled to RT and concentrated to
 dryness in vacuo. The residue was purified by flash
 chromatography (SiO_2 , 95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to afford 33 mg
 (80%) of the desired compound as a white foam. ^1H NMR
 25 (CDCl_3): 8.30 (s, 1H), 7.50 (d, 1H), 7.29 (d, 1H), 7.13
 (s, 1H), 7.09 (d, 2H), 6.84 (d, 1H), 6.78 (d, 2H), 6.37
 (d, 1H), 6.04 (s, 2H), 5.62 (d, 1H), 5.44 (br s, 1H),
 4.96 (m, 2H), 4.00 (t, 2H), 3.91 (m, 1H), 3.80 (m, 3H),
 3.71-3.49 (m, 5H), 3.18-2.65 (m, 7H), 2.08 (m, 2H), 1.80

-141-

(m, 1H), 1.61 (m, 1H), 1.50 (m, 1H), 0.90 (d, 3H), 0.81 (d, 3H). MS(ESI): 752 (M+H).

5

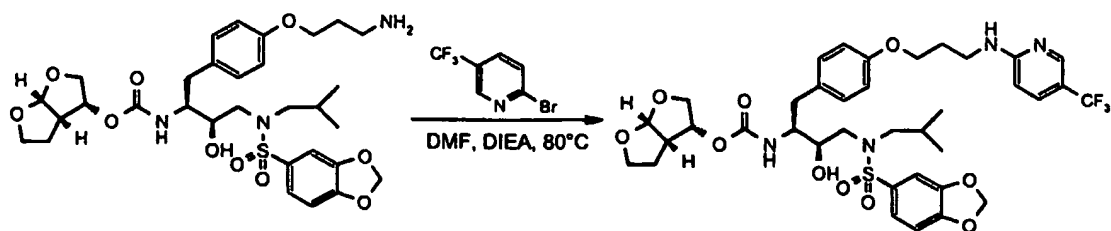
Example 60

10 (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-{4-[3-(2-pyrimidinylamino)propoxy]benzyl}
 propylcarbamate (271)
 The title compound was prepared according to example 270
 15 with the exception that 2-chloropyrimidine was used
 instead of 2-chloro-5-cyanopyridine. ¹H NMR (CDCl₃): 8.23
 (m, 2H), 7.29 (d, 1H), 7.12 (s, 1H), 7.06 (d, 2H), 6.86
 (d, 1H), 6.80 (d, 2H), 6.50 (t, 1H), 6.06 (s, 2H), 5.60
 (d, 1H), 5.50 (br s, 1H), 5.00 (m, 1H), 4.88 (d, 1H),
 20 4.00 (t, 2H), 3.92 (m, 1H), 3.80 (m, 3H), 3.71-3.52 (m,
 5H), 3.09 (m, 1H), 3.00-2.81 (m, 4H), 2.73 (m, 2H), 2.13-
 1.71 (m, 3H), 1.64 (m, 1H), 1.52 (m, 1H), 0.90 (d, 3H),
 0.83 (d, 3H). MS(ESI): 728 (M+H).

25

Example 61

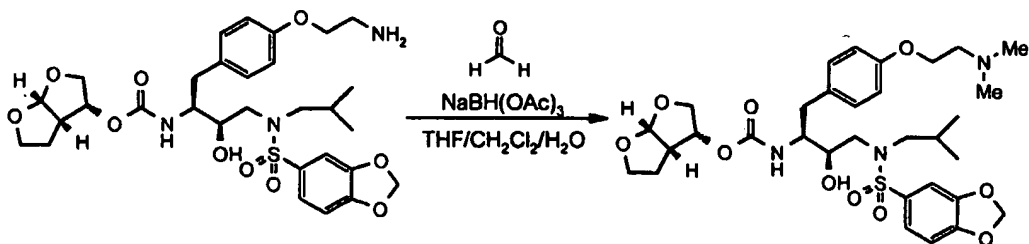
- 142 -



(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 5 hydroxy-1-[4-(3-{[5-(trifluoromethyl)-2-
 pyridinyl]amino}propoxy)benzyl]propylcarbamate (272)

The title compound was prepared according to example 270
 with the exception that 2-bromo-5-(trifluoromethyl)
 pyridine was used instead of 2-chloro-5-cyanopyridine. ¹H
 10 NMR (CDCl₃): 8.34 (s, 1H), 7.60 (d, 1H), 7.37 (d, 1H),
 7.21 (s, 1H), 7.16 (d, 2H), 6.93 (d, 1H), 6.86 (d, 2H),
 6.45 (d, 1H), 6.12 (s, 2H), 5.69 (d, 2H), 5.32 (br s,
 1H), 5.07 (m, 2H), 4.15-3.66 (m, 9H), 3.60 (m, 2H), 3.22-
 2.70 (m, 7H), 2.13 (m, 2H), 1.87 (m, 1H), 1.77-1.48 (m,
 15 2H), 0.98 (d, 3H), 0.91 (d, 3H). MS(ESI): 795(M+H).

Example 62



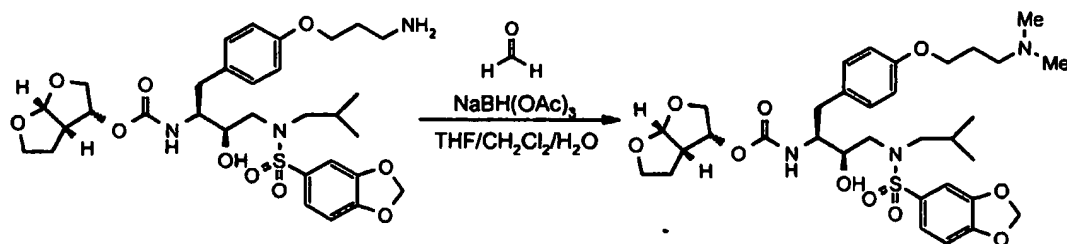
20

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-{4-[2-
 (dimethylamino)ethoxy]benzyl}-2-hydroxypropylcarbamate
 (273)

-143-

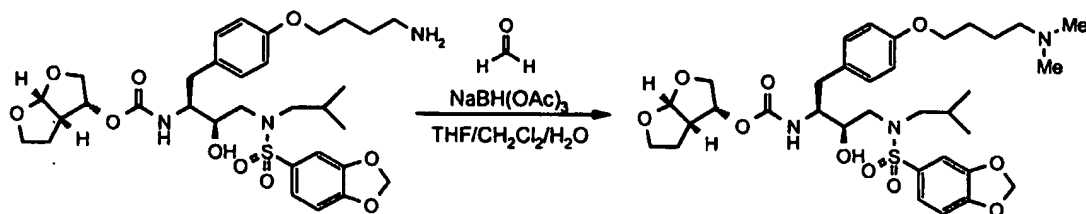
A solution of 21 mg (0.033 mmol) of (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-[4-(2-aminoethoxy)benzyl]-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxypropylcarbamate in 3 mL of 8:2 THF/CH₂Cl₂ was treated with 13 μL (0.17 mmol) of 37% aqueous formaldehyde followed by 35 mg (0.17 mmol) of NaBH(OAc)₃ and the resulting cloudy solution was stirred at RT. After 3 hours the solution was filtered to remove solids and the filtrate concentrated in vacuo. The residue was purified by flash chromatography (SiO₂, 95:5 CH₂Cl₂/2M NH₃ in MeOH) to give the desired compound as a white foam in 68% yield. ¹H NMR (CDCl₃): 7.29 (dd, 1H), 7.13 (s, 1H), 7.07 (d, 2H), 6.85 (d, 1H), 6.80 (d, 2H), 6.03 (s, 2H), 5.61 (d, 1H), 4.98 (q, 1H), 4.89 (d, 1H), 4.01 (t, 2H), 3.92 (m, 1H), 3.80 (m, 3H), 3.66 (m, 2H), 3.09 (dd, 1H), 2.92 (m, 5H), 2.74 (m, 4H), 2.32 (s, 6H), 1.80 (m, 1H), 1.63 (m, 1H), 1.42 (m, 1H), 0.90 (d, 3H), 0.84 (d, 3H). MS(ESI): 664 (M+H).

20

Example 63

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-[3-(dimethylamino)propoxy]benzyl]-2-hydroxypropylcarbamate (274)

According to example 273, (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-
 b]furan-3-yl (1*S*,2*R*)-1-[4-(3-aminopropoxy)benzyl]-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxypropylcarbamate was subjected to reductive
 5 alkylation with formaldehyde to give the desired compound
 as a white foam in 76% yield. ¹H NMR (CDCl₃): 7.37 (d,
 1H), 7.22 (s, 1H), 7.15 (d, 2H), 6.92 (d, 1H), 6.84 (d,
 2H), 6.13 (s, 2H), 5.70 (d, 1H), 5.07 (q, 1H), 4.95 (d,
 1H), 4.08-3.63 (m, 9H), 3.18 (dd, 1H), 3.00 (m, 4H), 2.82
 10 (m, 2H), 2.50 (t, 2H), 2.31 (s, 6H), 2.10-1.50 (m, 5H),
 0.97 (d, 3H), 0.91 (d, 3H). MS(ESI): 678(M+H).

Example 64

15

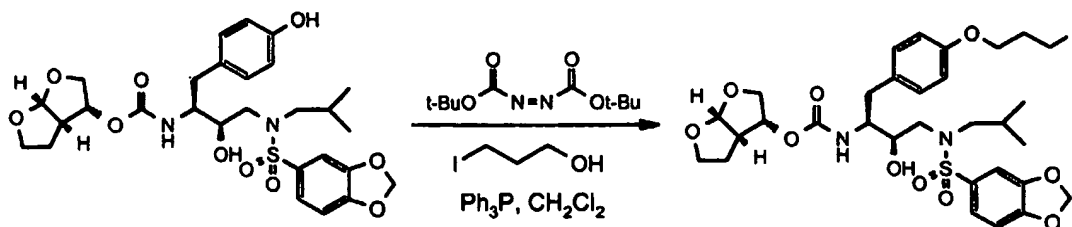
(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-{4-[4-
 20 (dimethylamino)butoxy]benzyl}-2-hydroxypropylcarbamate
 (275)

According to example 273, (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-
 b]furan-3-yl (1*S*,2*R*)-1-[4-(4-aminobutoxy)benzyl]-3-[(1,3-
 benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 25 hydroxypropylcarbamate was subjected to reductive
 alkylation with formaldehyde to give the desired compound
 as a white foam in 74% yield. ¹H NMR (CDCl₃): 7.37 (d,
 1H), 7.22 (s, 1H), 7.15 (d, 2H), 6.93 (d, 1H), 6.86 (d,
 2H), 6.12 (s, 2H), 5.69 (d, 1H), 5.07 (q, 1H), 4.94 (d,
 30 1H), 4.06-3.60 (m, 9H), 3.17 (dd, 1H), 3.00 (m, 4H), 2.81

-145-

(m, 2H), 2.40 (t, 2H), 2.32 (s, 6H), 1.95-1.50 (m, 7H), 0.98 (d, 3H), 0.91 (d, 3H). MS(ESI): 692 (M+H).

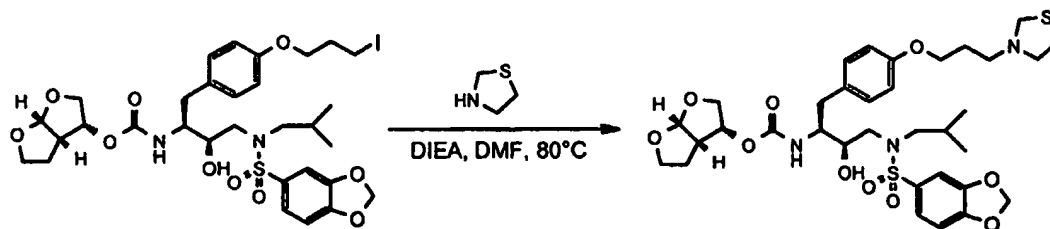
5

Example 65

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(3-iodopropoxy)benzyl]propylcarbamate (276)

The title compound was prepared according to example 202
 with the exception that 3-iodo-1-propanol was used
 instead of phenethyl alcohol. ¹H NMR (CDCl₃): 7.29 (d,
 1H), 7.13 (s, 1H), 7.09 (d, 2H), 6.86 (d, 1H), 6.78 (d,
 2H), 6.04 (s, 2H), 5.61 (d, 1H), 4.99 (q, 1H), 4.85 (d,
 1H), 3.94 (m, 3H), 3.80 (m, 3H), 3.67 (m, 2H), 3.55 (m,
 1H), 3.32 (t, 2H), 3.09 (dd, 1H), 3.92 (m, 4H), 2.73 (m,
 2H), 2.21 (m, 2H), 1.80 (m, 1H), 1.63 (m, 1H), 1.49 (m,
 1H), 0.90 (d, 3H), 0.83 (d, 3H). MS(ESI): 761 (M+H).

20

Example 66

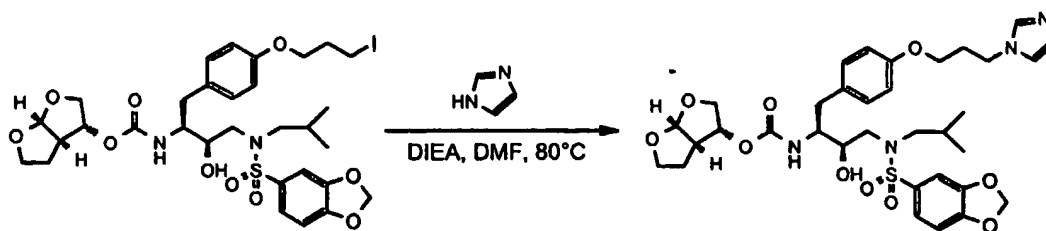
25

-146-

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-[3-(1,3-thiazolidin-3-yl)propoxy]
 benzyl}propylcarbamate (277)

- 5 A solution of 35 mg (0.046 mmol) of (3R,3aS,6aR)-
 hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-
 benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-[4-
 (3-iodopropoxy)benzyl}propylcarbamate, 11 μ L (0.14 mmol)
 of thiazolidine, and 32 μ L (0.18 mmol) of *N,N*-
 10 diisopropylethylamine in 0.5 mL of anhydrous DMF was
 heated to 80°C with stirring. After 1.5 hours TLC
 indicated the reaction to be complete. The solution was
 cooled to RT and concentrated *in vacuo*. The residue was
 subjected to flash chromatography (SiO₂, 95:5 CH₂Cl₂/MeOH)
 15 to afford 22 mg (67%) of the desired compound as a white
 foam. ¹H NMR (CDCl₃): 7.29 (d, 1H), 7.13 (s, 1H), 7.08
 (d, 2H), 7.85 (d, 1H), 6.77 (d, 2H), 6.04 (s, 2H), 5.60
 (d, 1H), 5.00 (q, 1H), 4.88 (d, 1H), 4.01 (s, 2H), 4.00-
 3.88 (m, 3H), 3.80 (m, 3H), 3.67 (m, 2H), 3.55 (br s,
 20 1H), 3.19-3.01 (m, 4H), 3.00-2.65 (m, 7H), 2.52 (t, 2H),
 1.93 (m, 2H), 1.79 (m, 1H), 1.70-1.42 (m, 2H), 0.89 (d,
 3H), 0.83 (d, 3H). MS(ESI): 722 (M+H).

Example 67



25

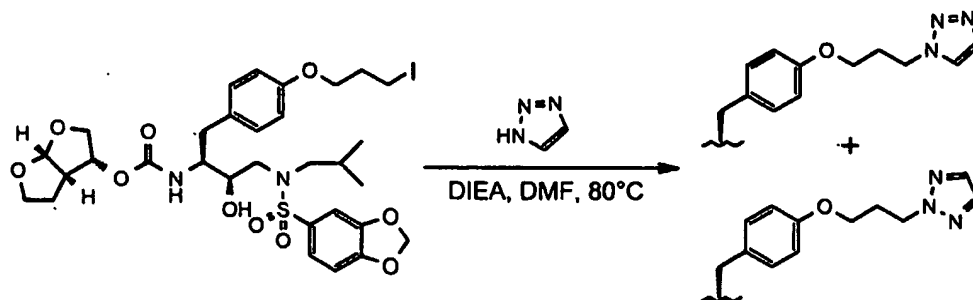
(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-

-147-

hydroxy-1-{4-[3-(1*H*-imidazol-1-yl)propoxy]benzyl}
propylcarbamate (278)

The title compound was prepared according to example 66
with the exception that imidazole was substituted for
5 thiazolidine. ¹H NMR (CDCl₃): 7.54 (s, 1H), 7.38 (d, 1H),
7.21 (s, 1H), 7.17 (d, 2H), 7.11 (s, 1H), 6.92 (m, 2H),
6.82 (d, 2H), 6.13 (s, 2H), 5.70 (d, 1H), 5.09 (m, 2H),
4.22 (t, 2H), 4.07-3.68 (m, 8H), 3.22-2.73 (m, 8H), 2.25
(m, 2H), 1.88 (m, 1H), 1.77-1.55 (m, 2H), 0.93 (m, 6H).
10 MS(ESI): 701 (M+H).

Example 68



15

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
hydroxy-1-{4-[3-(1*H*-1,2,3-triazol-1-
yl)propoxy]benzyl}propylcarbamate and (3*R*,3*aS*,6*aR*)-
20 hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-
benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-{4-
[3-(2*H*-1,2,3-triazol-2-yl)propoxy]benzyl}propylcarbamate
(279)

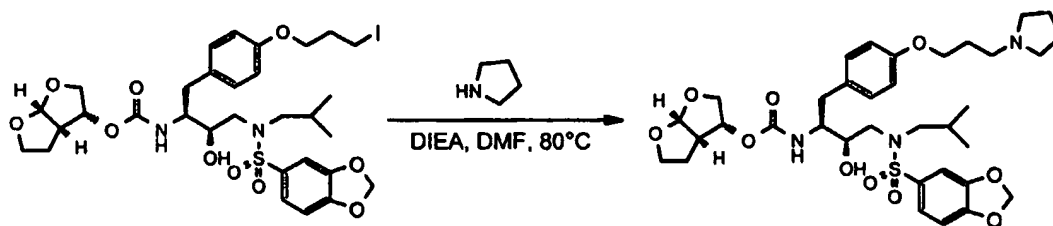
According to example 66, (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-
25 *b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-
ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-[4-(3-
iodopropoxy)benzyl]propylcarbamate was reacted with

-148-

1,2,3-triazole to afford an approximately 1:1 mixture of triazole isomers (as determined by ^1H -NMR and HPLC).

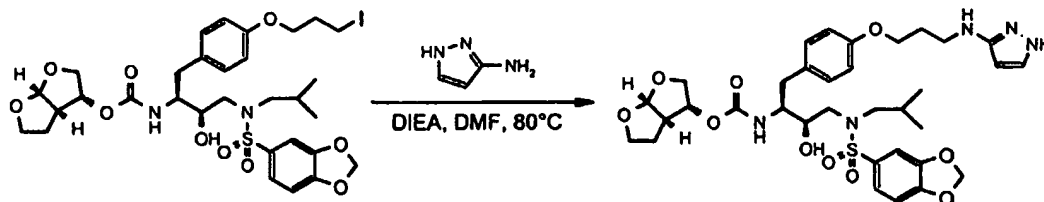
MS(ESI): 702 (M+H).

5

Example 69

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 10 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-{4-[3-(1-pyrrolidinyl)propoxy]benzyl}
 propylcarbamate (280)

The title compound was prepared according to example 66 with the exception that pyrrolidine was substituted for
 15 thiazolidine. ^1H NMR (CDCl_3): 7.36 (d, 1H), 7.21 (s, 1H),
 7.13 (d, 2H), 6.92 (d, 1H), 6.83 (d, 2H), 6.12 (s, 2H),
 5.68 (d, 1H), 5.02 (m, 2H), 4.00 (m, 3H), 3.93-3.62 (m,
 6H), 3.15 (dd, 1H), 3.00 (m, 4H), 2.88-2.61 (m, 8H), 2.10
 (m, 2H), 1.88 (m, 5H), 1.78-1.50 (m, 2H), 0.96 (d, 3H),
 20 0.91 (d, 3H). MS(ESI): 704 (M+H).

Example 70

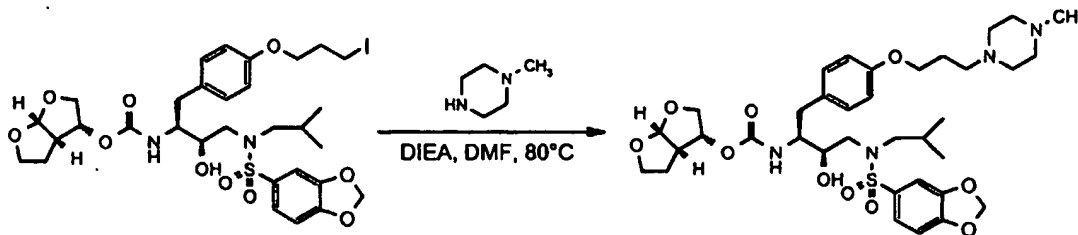
25

-149-

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-{4-[3-(1H-pyrazol-3-ylamino)propoxy]benzyl}
 propylcarbamate (281)

- 5 The title compound was prepared according to example 66
 with the exception that 3-aminopyrazole was substituted
 for thiazolidine. ¹H NMR (CDCl₃): 7.28 (m, 2H), 7.14 (s,
 1H), 7.05 (d, 2H), 6.84 (d, 1H), 6.75 (d, 2H), 6.03 (s,
 2H), 5.58 (m, 2H), 5.15 (d, 1H), 4.99 (q, 1H), 4.80-4.20
 10 (br s, 2H), 4.00 (t, 2H), 3.90 (dd, 1H), 3.78 (m, 3H),
 3.67 (m, 2H), 3.31 (t, 2H), 3.08 (m, 1H), 3.01-2.63 (m,
 7H), 2.01 (m, 2H), 1.80 (m, 1H), 1.61 (m, 1H), 1.47 (m,
 1H), 0.88 (d, 3H), 0.81 (d, 3H). MS(ESI): 716 (M+H).

15

Example 71

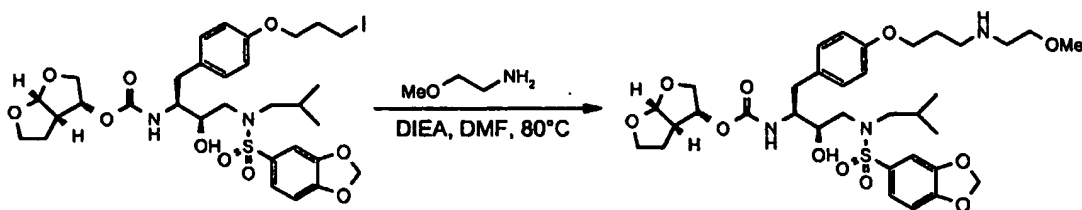
- 20 (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-{4-[3-(4-methyl-1-piperazinyl)propoxy]
 benzyl}propylcarbamate (282)

- The title compound was prepared according to example 66
 25 with the exception that 1-methylpiperazine was
 substituted for thiazolidine. ¹H NMR (CDCl₃): 7.37 (d,
 1H), 7.20 (s, 1H), 7.14 (d, 2H), 6.92 (d, 1H), 6.84 (d,
 2H), 6.12 (s, 2H), 5.68 (d, 1H), 5.14-4.92 (m, 2H), 4.00
 (m, 3H), 3.86 (m, 3H), 3.72 (m, 3H), 3.16 (dd, 1H), 3.08-

-150-

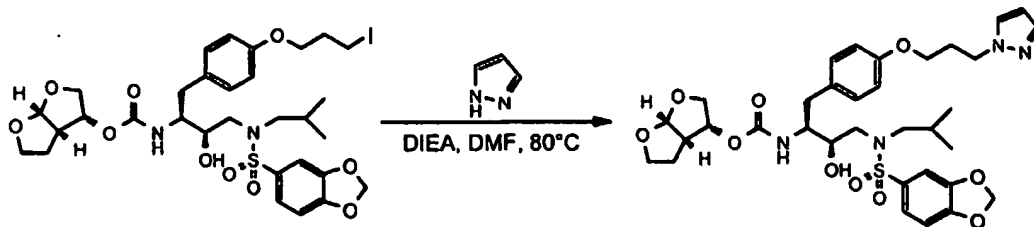
2.90 (m, 4H), 2.89-2.39 (m, 12H), 2.33 (s, 3H), 2.00 (m, 2H), 1.87 (m, 1H), 1.68 (m, 1H), 1.52 (m, 1H), 0.98 (d, 3H), 0.91 (d, 3H). MS(ESI): 733 (M+H).

5

Example 72

10 (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-(4-{3-[(2-methoxyethyl)amino]propoxy}benzyl)
 propylcarbamate (283)

The title compound was prepared according to example 66
 15 with the exception that 2-methoxyethylamine was
 substituted for thiazolidine. ¹H NMR (CDCl₃): 7.38 (d,
 1H), 7.20 (s, 1H), 7.14 (d, 2H), 6.91 (d, 1H), 6.86 (d,
 2H), 6.12 (s, 2H), 5.69 (d, 1H), 5.13-4.90 (m, 2H), 4.01
 (m, 3H), 3.87 (m, 3H), 3.74 (m, 3H), 3.52 (t, 2H), 3.40
 20 (s, 3H), 3.18 (dd, 1H), 3.00 (m, 4H), 2.81 (m, 7H), 2.08-
 1.50 (m, 5H), 0.98 (d, 3H), 0.91 (d, 3H). MS(ESI):
 708 (M+H).

Example 73

25

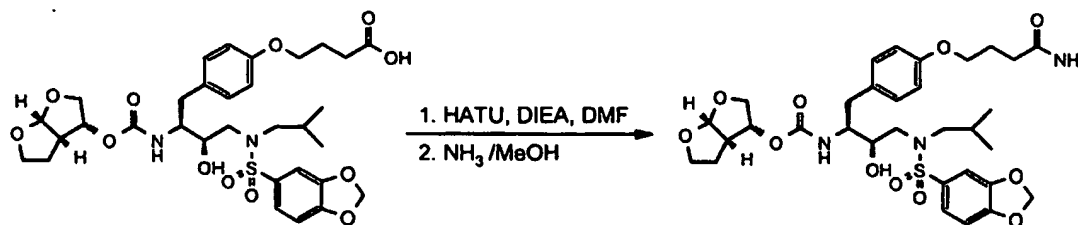
(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-{4-[3-(1H-pyrazol-1-yl)propoxy]benzyl}

5 **propylcarbamate (284)**

The title compound was prepared according to example 66
 with the exception that pyrazole was substituted for
 thiazolidine. ¹H NMR (CDCl₃): 7.50 (s, 1H), 7.32 (s, 1H),
 7.29 (d, 1H), 7.13 (s, 1H), 7.08 (d, 2H), 6.85 (d, 1H),
 10 6.76 (d, 2H), 6.20 (s, 1H), 6.06 (s, 2H), 5.61 (d, 1H),
 5.00 (q, 1H), 4.88 (d, 1H), 4.33 (t, 2H), 3.92 (dd, 1H),
 3.80 (m, 5H), 3.68 (m, 2H), 3.58 (br s, 1H), 3.09 (dd,
 1H), 2.90 (m, 4H), 2.73 (m, 2H), 2.28 (m, 2H), 1.85-1.43
 (m, 3H), 0.89 (d, 3H), 0.82 (d, 3H). MS(ESI): 701(M+H).

15

Example 74



20 **(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-[4-
 (4-amino-4-oxobutoxy)benzyl]-3-[(1,3-benzodioxol-5-
 ylsulfonyl)(isobutyl)amino]-2-hydroxypropylcarbamate
 (285)**

A solution of 25 mg (0.037 mmol) of 4-(4-{(2S,3R)-2-
 25 {[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-
 yloxy]carbonyl}amino)-4-[(1,3-benzodioxol-5-
 ylsulfonyl)(isobutyl)amino]-3-
 hydroxybutyl}phenoxy)butanoic acid and 19 μ L (0.11 mmol)
 of *N,N*-diisopropylethylamine in 1 mL of anhydrous DMF was

-152-

treated with 28 mg (0.074 mmol) of *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU). The resulting solution was stirred at RT for 15 minutes and was then treated with 0.5 mL of 2M NH₃ in MeOH. After 20 minutes TLC indicated the reaction to be complete. The solution was concentrated to dryness at reduced pressure and the residue subjected to flash chromatography (SiO₂, 95:5 CH₂Cl₂/2M NH₃ in MeOH) to afford 11 mg (44%) of the desired compound as a white powder. ¹H NMR (CDCl₃): 7.30 (d, 1H), 7.14 (s, 1H), 7.07 (d, 2H), 6.85 (d, 2H), 6.75 (d, 2H), 6.05 (s, 2H), 5.60 (d, 1H), 5.56-5.34 (m, 2H), 4.97 (m, 2H), 3.94 (m, 3H), 3.78 (m, 3H), 3.66 (m, 2H), 3.09 (m, 1H), 3.00-2.64 (m, 7H), 2.40 (t, 2H), 2.08 (m, 2H), 1.80 (m, 1H), 1.61 (m, 1H), 1.48 (m, 1H), 0.90 (d, 3H), 0.82 (d, 3H). MS(ESI): 678(M+H).

Example 75

20

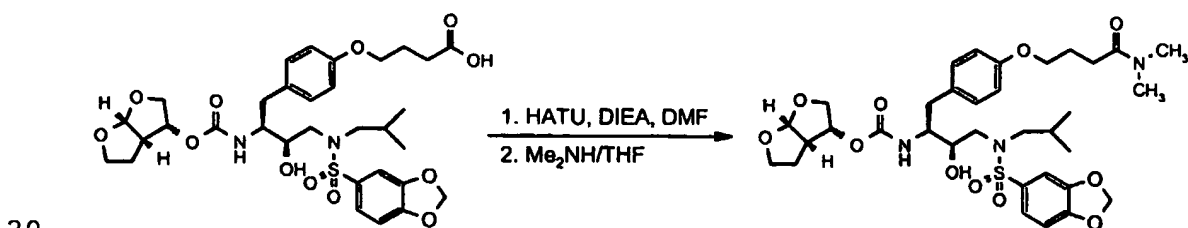
(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-[4-[4-(methoxycarbonyl)-4-oxobutoxy]benzyl]propylcarbamate (286)

25

A solution of 35 mg (0.052 mmol) of 4-(4-[(2*S*,3*R*)-2-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-3-

hydroxybutyl}phenoxy)butanoic acid and 27 μ L (0.16 mmol) of *N,N*-diisopropylethylamine in 1 mL of anhydrous DMF was treated with 49 mg (0.13 mmol) of *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU). The resulting solution was stirred at RT for 15 minutes and was then treated with 0.5 mL of 8M MeNH₂ in EtOH. After 18 hours TLC indicated the reaction to be complete. The solution was concentrated to dryness at reduced pressure and the residue subjected to flash chromatography (SiO₂, 95:5 CH₂Cl₂/MeOH) to afford 22 mg (61%) of the desired compound as a white powder. ¹H NMR (CDCl₃): 7.37 (d, 1H), 7.22 (s, 1H), 7.13 (d, 2H), 6.92 (d, 1H), 6.82 (d, 2H), 6.13 (s, 2H), 5.67 (m, 2H), 5.05 (m, 2H), 4.00 (m, 3H), 3.88 (m, 3H), 3.72 (m, 2H), 3.24-2.71 (m, 11H), 2.40 (t, 2H), 2.16 (m, 2H), 1.88 (m, 1H), 1.67 (m, 1H), 1.53 (m, 1H), 0.94 (m, 6H). MS(ESI): 692 (M+H).

Example 76



(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-{4-[4-(dimethylamino)-4-oxobutoxy]benzyl}-2-hydroxypropylcarbamate (287)

25

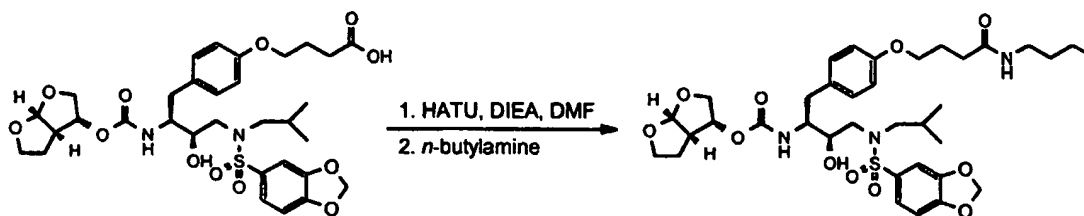
The title compound was prepared according to example 286 with the exception that 1 mL of 2M Me₂NH/THF was substituted for MeNH₂/EtOH. ¹H NMR (CDCl₃): 7.36 (d, 1H), 7.21 (s, 1H), 7.13 (d, 2H), 0.92 (d, 1H), 6.85 (d, 2H),

-154-

6.12 (s, 2H), 5.69 (d, 1H), 5.02 (m, 2H), 4.01 (m, 3H),
3.87 (m, 3H), 3.73 (m, 2H), 3.16 (dd, 1H), 3.10-2.88 (m,
11H), 2.81 (m, 2H), 2.54 (t, 2H), 2.16 (m, 2H), 1.86 (m,
1H), 1.79-1.50 (m, 2H), 0.98 (d, 3H), 0.90 (d, 3H).

5 MS (ESI): 706 (M+H).

Example 77



10 (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-{4-[4-
(butylamino)-4-oxobutoxy]benzyl}-2-hydroxypropylcarbamate
(288)

The title compound was prepared according to example 286

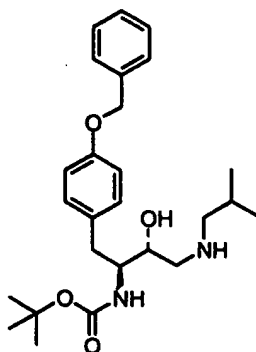
15 with the exception that 60 μ L of *n*-butylamine was
substituted for MeNH₂/EtOH. ¹H NMR (CDCl₃): 7.38 (d, 1H),
7.21 (s, 1H), 7.14 (d, 2H), 6.93 (d, 1H), 6.84 (d, 2H),
6.12 (s, 2H), 5.69 (d, 1H), 5.60 (br s, 1H), 5.03 (m,
2H), 4.00 (m, 3H), 3.87 (m, 3H), 3.73 (m, 2H), 3.39-2.72
20 (m, 10H), 2.39 (t, 2H), 2.13 (m, 2H), 1.88 (m, 1H), 1.69
(m, 1H), 1.60-1.27 (m, 5H), 0.93 (m, 9H). MS (ESI):
734 (M+H).

Example 78

25 Step 1:

t-Butyl-(1S,2R)-1-(4-benzyloxy-benzyl)-3-*i*-butylamino-2-
hydroxypropyl-carbamate

-155-



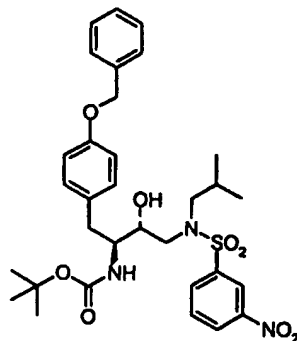
i-Butylamine (7.0 g, 94.7 mmol) was added to a solution
5 of *t*-butyl-(1*S*,2*R*)-1-(4-benzyloxy-benzyl)-2,3-epoxydo-
propyl-carbamate (5.0 g, 13.5 mmol) (prepared according
to the reference by Chen, P. at all., *Tetrahedron Letters*
1997, 38, 3175-3178), in *i*-propanol (70 mL). The mixture
was stirred at 85°C for 2 hours, then cooled to 5°C. Water
10 (400 mL) was added dropwise. The resulting suspension was
stirred for 30 minutes at 5°C, then filtered. The solid
was washed with water (3x100 mL), and dried *in vacuo* to
yield title product (5.5 g, 92%).

15 ¹H NMR (CDCl₃): δ 0.88 (6H, d), 1.34 (9H, s), 1.68 (1H,
m), 2.38 (2H, d), 2.64 (2H, d), 2.80 (1H, m), 2.86 (1H,
dd), 3.40 (1H, m), 3.70 (2H, broad s), 4.63 (1H, d), 5.01
(2H, s), 6.88 (2H, d), 7.12 (2H, d), 7.40 (5H, m).

20 Step 2:

-156-

t-Butyl-N((1*S*,2*R*)-1-(4-benzyloxy-benzyl)-3-*i*-butyl-[(3-nitrobenzene)sulfonyl]-amino-2-hydroxypropyl)-carbamate



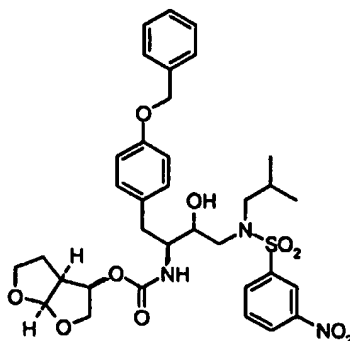
A CH₂Cl₂ (50 mL) solution of the product from Step 1 (1.7 g, 3.8 mmol), 3-nitrobenzenesulfonylchloride (1.1 g, 4.8 mmol), and diisopropylethylamine (1.0 g, 7.8 mmol) was stirred at 20°C for 4 hours. Water (70 mL) was then added to the reaction mixture and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (3x100 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was dissolved in ether (300 mL), and silicagel (50 g) was added to the solution. The mixture was then filtered. The filtrate was concentrated under reduced pressure. The residue was added hexane (300 mL), stirred for three hours at 20°C, and then the white solid was filtered and dried to afford title compound (1.9 g, 80%).

¹H NMR (CDCl₃): δ 0.88 (6H, d), 1.35 (9H, s), 1.86 (1H, m), 2.85 (2H, m), 2.99 (2H, d), 3.19 (2H, d), 3.77 (2H, m), 4.57 (1H, d), 5.03 (2H, s), 6.90 (1H, d), 7.12 (1H, d), 7.40 (5H, m), 7.69 (1H, t), 8.08 (1H, d), 8.39 (1H, d), 8.62 (1H, s).

Step 3:

-157-

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-benzyloxy-benzyl)-3-*i*-butyl-[(3-nitrobenzene)sulfonyl]-amino-2-hydroxypropyl)-carbamate



5

Trifluoroacetic acid (15 mL) was added dropwise to a solution of the product from Step 2 (1.5 g, 5 mmol) in CH₂Cl₂ (40 mL). The mixture was stirred for 1 hour at 20°C, then concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (200 mL) and 10% aqueous Na₂CO₃ solution (100 mL) was added. The mixture was stirred at 20°C for 15 minutes. Phases were separated, and the aqueous phase was extracted with additional CH₂Cl₂ (2x50 ml). The combined organic phases were then dried over Na₂CO₃ and concentrated under reduced pressure. The residue was dissolved in acetonitrile (40 mL). Diisopropylethylamine (2.0 g, 15.3 mmol) and (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl-4-nitrophenyl carbonate (2.0 g, 6.7 mmol) were added, and the solution was stirred for 12 hours at 20°C. Then 25% aqueous ammonium hydroxide solution (6 mL) was added, and the mixture was stirred for an additional 0.5 hour. The solvents were removed under reduced pressure. The residue was dissolved in EtOAc (100 mL), and the solution was

-158-

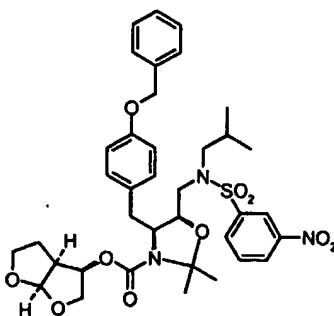
extracted with 5% aqueous Na_2CO_3 solution (10x75 mL) and washed with brine (1x75 mL). The organic phase was dried over Na_2CO_3 , and concentrated in vacuo. Hexane (30 mL) was added to the residue and the mixture was stirred at 20°C for 1 hour. Then the white solid was filtered and air dried to yield title compound (1.5 g, 60%).

^1H NMR (CDCl_3): δ 0.86 (3H, d), 0.88 (3H, d), 1.54 (1H, m), 1.65 (1H, m), 1.85 (1H, m), 2.75 (1H, m), 2.97 (4H, m), 3.14 (2H, m), 3.37 (1H, m), 3.68 (2H, m), 3.82 (2H, m), 3.94 (2H, m), 4.85 (1H, d), 5.00 (3H, s), 5.60 (1H, d), 6.88 (2H, d), 7.09 (2H, d), 7.35 (5H, m), 7.72 (1H, t), 8.07 (1H, d), 8.38 (1H, d), 8.61 (1H, s); MS: 684 (M^+).

15

Step 4:

N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-oxycarbonyl-(4S,5R)-4-(4-benzyloxy-benzyl)-5-i-butyl-[(3-nitrobenzene)sulfonyl]-aminomethyl-2,2-dimethyl-oxazolidine



A CH_2Cl_2 (8 mL) solution of the product of Step 3 (0.5 g, 0.7 mmol) was added 2,2-dimethoxy-propane (0.8 mL, 6.5 mmol) and *p*-toluenesulfonic acid (40 mg, 0.2 mmol). The mixture was refluxed for 4 hours, cooled to 20°C, and washed with 5% aqueous Na_2CO_3 solution (10 mL). The

organic phase was dried over MgSO_4 , filtered, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 using hexane-EtOAc (1:1) as eluent, to provide title compound (0.5 g, 95%).

5

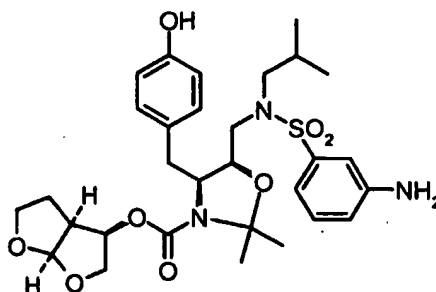
¹H NMR (CDCl₃): δ 0.83 (3H, d), 0.91 (3H, d), 1.33, 1.40 (3H, s)*, 1.50, 1.57 (3H, s)*, 1.85 (2H, m), 1.97 (1H, m), 2.70 (3H, m), 3.10 (3H, m), 3.22 (1H, d), 3.36 (1H, d), 3.43 (1H, m), 3.80 (2H, m), 3.94 (1H, m), 4.21 (2H, m), 5.03 (2H, s), 5.65, 5.68 (1H, d)*, 6.87 (2H, d), 7.02 (1H, d), 7.38 (5H, m), 7.62 (1H, t), 7.85 (1H, d), 8.35 (1H, t), 8.54 (1H, s); MS: 724 (M⁺).

*possible indication for rotamers.

15

Step 5:

N- (3R, 3aS, 6aR) -Hexahydrofuro [2, 3-b] furan-3-yl-oxycarbonyl- (4S, 5R) -4- (4-hydroxybenzyl) -5-*i*-butyl- [(3-aminobenzene) sulfonyl] -aminomethyl-2, 2-dimethyl-oxazolidine



Pd/C (10% Pd, Degussa type) (0.5 g) was added to a THF (10 mL) solution of the product of Step 4 (0.5 g, 0.7 mmol). The mixture was hydrogenated under atmospheric pressure H₂ for 12 hours. The catalyst was removed by

-160-

filtration through Celite, and the solvent was evaporated in vacuo. The residue was triturated in hexane. The white solid was then filtered and washed with hexane (2x20 ml) to afford title compound (210 mg, 50%).

5

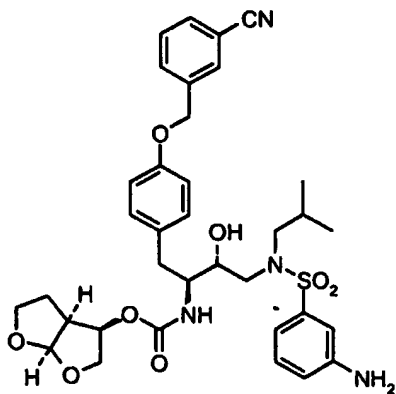
¹H NMR (DMSO-d₆): δ 0.80 (6H, m), 1.22, 1.35 (3H, s)*, 1.45, 1.53 (3H, s)*, 1.75 (2H, m), 1.95 (1H, m), 2.50-3.30 (10H, m), 3.60 (2H, d), 3.80 (1H, m), 4.06 (1H, m), 4.74 (1H, dd), 5.52 (2H, d), 6.65 (3H, m), 6.90 (3H, m), 7.12 (1H, t), 9.22 (1H, s); MS: 604 (M⁺).

10

*possible indication for rotamers.

Step 6:

15 (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-[4-(3-cyanobenzyloxy)-benzyl]-3-*i*-butyl-[(3-aminobenzene)sulfonyl]-amino-2-hydroxypropyl)-carbamate (289)



20

Cs₂CO₃ (134.4 mg, 0.4 mmol) and 3-(bromomethyl)benzonitrile (65 mg, 0.3 mmol) were added to the product of Step 5 (200 mg, 0.3 mmol) in DMF (2 mL). The mixture was stirred at 20°C for 4 hours, diluted with

-161-

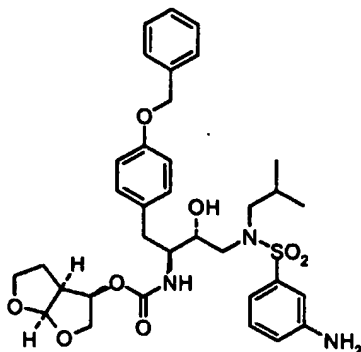
Et₂O (50 mL), and filtered. The filtrate was washed with water (1x35 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue, dissolved in 1,4-dioxane (6 mL), was added 4 M HCl in dioxane (7.5 ml) and water (0.2 g). The solution was stirred at 20°C for 2 hours and then diluted with water (50 mL). A solution of 5% aqueous Na₂CO₃ was added until pH 12-14, and the mixture was extracted with CH₂Cl₂ (3x20 mL). The combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was chromatographed on SiO₂ using EtOAc-hexane (4:1) as eluent to afford title compound (85 mg, 45%).

¹H NMR (DMSO-d₆): δ 0.78 (3H, d), 0.83 (3H, d), 1.25 (2H, m), 1.34 (1H, m), 1.90 (1H, m), 2.36 (1H, t), 2.71 (3H, m), 2.93 (2H, m), 3.54 (4H, m), 3.66 (1H, t), 3.80 (1H, dd), 4.80 (1H, dd), 4.95 (1H, d), 5.08 (2H, s), 5.47 (1H, d), 5.53 (2H, s), 6.73 (1H, d), 6.80 (1H, d), 6.84 (2H, d), 6.92 (1H, s), 7.10 (2H, d), 7.15 (2H, t), 7.57 (1H, t), 7.75 (2H, t), 7.85 (1H, s); MS: 679 (M⁺).

Example 79

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-benzyloxy-benzyl)-3-*i*-butyl-[(3-aminobenzene)sulfonyl]-amino-2-hydroxypropyl-carbamate (290)

-162-



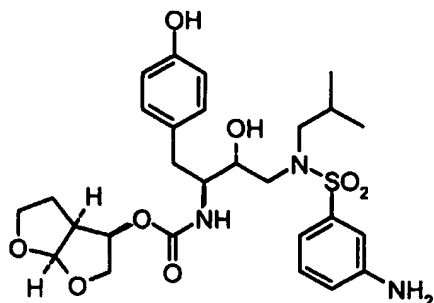
(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-benzyloxy-benzyl)-3-i-butyl-[(3-
 5 nitrobenzene)sulfonyl]-amino-2-hydroxypropyl)-carbamate
 (100 mg, 0.15 mmol) in THF (3 mL) was added Pt/C (3% Pt)
 (30 mg). The mixture was hydrogenated under atmospheric
 pressure H₂ for 12 hours. The catalyst was removed by
 filtration through Celite, and the solvent was evaporated
 10 in vacuo to yield title compound (60 mg, 65%).

¹H NMR (CDCl₃): δ 0.82 (3H, d), 0.89 (3H, d), 1.22 (1H, m), 1.60 (1H, m), 1.81 (2H, m), 2.77 (2H, m), 2.97 (4H, m), 3.15 (1H, m), 3.64 (3H, m), 3.82 (3H, m), 3.95 (1H, m), 4.96 (1H, d), 5.02 (3H, d), 5.63 (1H, d), 6.80 (1H, d), 6.88 (2H, d), 6.96 (3H, m), 7.08 (3H, m), 7.12 (1H, m), 7.35 (4H, m); MS: 654 (M⁺).

Example 80

20 (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-hydroxybenzyl)-3-i-butyl-[(3-aminobenzene)sulfonyl]-amino-2-hydroxypropyl)-carbamate (291)

-163-



(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-
 5 (4-benzyloxy-benzyl)-3-i-butyl-[(3-nitrobenzene)sulfonyl]-amino-2-hydroxypropyl)-carbamate
 (300 mg, 0.44 mmol) in THF (8 mL) was added Pd/C (10% Pd, Degussa Type) (300 mg). The mixture was hydrogenated under atmospheric pressure H₂ for 12 hours. The catalyst
 10 was removed by filtration through Celite, and the solvent was evaporated in vacuo to yield title compound (95 mg, 50%).

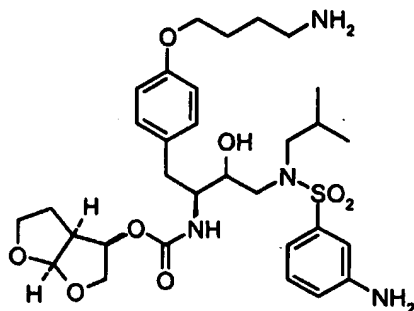
¹H NMR (DMSO-d₆): δ 0.75 (3H, d), 0.82 (3H, d), 1.25 (2H, m),
 15 1.40 (1H, m), 1.93 (1H, m), 2.32 (1H, t), 2.72 (3H, m), 2.85 (1H, d), 2.95 (1H, m), 3.55 (4H, m), 3.71 (1H, t), 3.81 (1H, dd), 4.82 (1H, dd), 4.92 (1H, m), 5.48 (1H, d), 5.53 (2H, s), 6.56 (2H, d), 6.73 (1H, d), 6.79 (1H, d), 6.94 (3H, m), 7.14 (2H, m), 9.00 (1H, s).

20

Example 81

-164-

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-(butylamine)benzyl)-3-*i*-butyl-[(3-aminobenzene)sulfonyl]-amino-2-hydroxypropyl-carbamate (292)



5

t-Butyl-*N*-(4-hydroxybutyl)carbamate (75.7 mg, 0.40 mmol) and triphenylphosphine (105 mg, 0.40 mmol) were mixed in CH₂Cl₂ (5 mL) and stirred at 0°C for 30 minutes. Di-*t*-butyl azodicarboxylate (92.1 mg, 0.40 mmol) was then added, followed by (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-hydroxybenzyl)-3-*i*-butyl-[(3-aminobenzene)sulfonyl]-amino-2-hydroxypropyl-carbamate (90 mg, 0.16 mmol). The mixture was stirred at 20°C for 12 hours. The solvent was then evaporated, and the residue was chromatographed on SiO₂ using EtOAc-hexane (4:1) as eluent. The isolated intermediate was dissolved in CH₂Cl₂ (16 mL). TFA (4 mL) was added. The mixture was stirred for 2 hours at room temperature, and concentrated to afford title compound (65 mg, 50%) as a TFA salt.

20

¹H NMR (DMSO-*d*₆): δ 0.75 (3H, d), 0.82 (3H, d), 1.20 (2H, m), 1.38 (1H, m), 1.60 (6H, m), 1.90 (1H, m), 2.38 (1H, t), 2.75 (3H, m), 2.92 (1H, m), 3.37 (2H, m), 3.72 (1H, t), 3.82 (1H, dd), 3.90 (1H, m), 4.37 (1H, t), 4.80 (1H, dd), 5.48 (1H, d), 6.77 (3H, m), 6.85 (1H, d), 6.97 (1H,

25

-165-

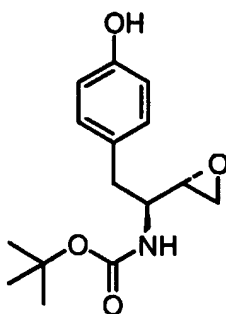
s), 7.09 (2H, d), 7.16 (2H, dd), 7.65 (2H, broad s); MS: 635 (M⁺).

5

Example 82

Step 1:.

t-Butyl-(1S,2R)-1-(4-hydroxybenzyl)-2,3-epoxydo-propyl-carbamate



10

Pd(OH)₂/C (20% Pd, Degussa Type) (70 mg) was added to a solution of t-butyl-(1S,2R)-1-(4-benzyloxy-benzyl)-2,3-epoxydo-propyl-carbamate (700 mg, 1.9 mmol) (prepared according to the reference by Chen, P. at all.,
15 *Tetrahedron Letters* 1997, 38, 3175-3178) in EtOH (12 mL) and EtOAc (3 mL). The mixture was hydrogenated under atmospheric pressure H₂ for 2 hours, filtrated through Celite, and concentrated to yield title compound (530 mg, 100%).

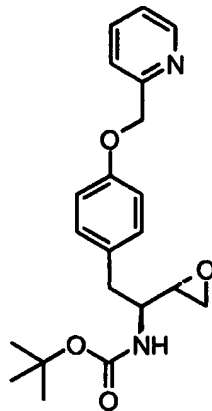
20

¹H NMR (DMSO-d₆): δ 1.25 (9H, s), 2.55 (4H, m), 2.82 (1H, m), 3.36 (1H, m), 6.60 (2H, d), 6.75 (1H, d), 6.95 (2H, d), 9.09 (1H, s).

25 **Step 2:**

-166-

***t*-Butyl-(1*S*,2*R*)-1-(4-(2-pyridylmethoxy)benzyl)-2,3-epoxydo-propyl-carbamate**



5 Cs_2CO_3 (1.60 g, 5.05 mmol) in DMF (10 mL) was added 2-picolylchloride hydrochloride (400 mg, 2.44 mmol). After stirring for 5 minutes at room temperature, *t*-Butyl-(1*S*,2*R*)-1-(4-hydroxybenzyl)-2,3-epoxydo-propyl-carbamate (450 mg, 1.61 mmol) was added. The mixture was stirred
10 for an additional 2 hours at 20°C, diluted with Et_2O (50 mL), and filtered. The filtrate was washed with water, dried over MgSO_4 , and concentrated. The residue was chromatographed on silicagel using EtOAc-hexane (3:2) as eluent to afford title compound (505 mg, 85%).

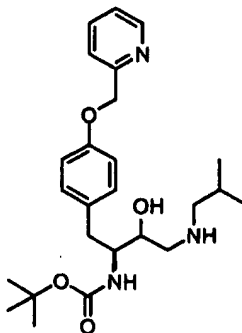
15

^1H NMR ($\text{DMSO}-d_6$): δ 1.22 (9H, s), 2.45 (1H, s), 2.62 (1H, m), 2.74 (1H, dd), 2.84 (1H, m), 3.42 (1H, m), 5.08 (2H, s), 6.79 (1H, d), 6.87 (2H, d), 7.07 (2H, d), 7.28 (1H, dd), 7.44 (1H, d), 7.78 (1H, t), 8.52 (1H, d); MS: 371
20 (M^+).

Step 3:

-167-

***t*-Butyl-(1*S*,2*R*)-1-(4-(2-pyridylmethoxy)benzyl)-3-*i*-butylamino-2-hydroxypropyl-carbamate**

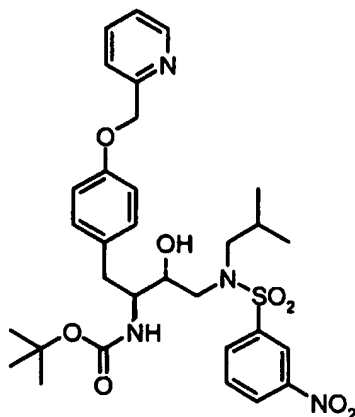


i-Butylamine (610 mg, 8.33 mmol) was added to a solution of *t*-Butyl-(1*S*,2*R*)-1-(4-(2-pyridylmethoxy)benzyl)-2,3-epoxydo-propyl-carbamate (440 mg, 1.20 mmol) in *i*-propanol (10 mL). The mixture was then stirred at 85°C for 2 hours, cooled to 5°C, diluted with water (75 mL), and extracted with CHCl₃ (4x70 mL). The combined organic phases were dried over MgSO₄, filtered, and concentrated to afford title product (320 mg, 60%).

¹H NMR (CDCl₃): δ 0.87 (6H, d), 1.33 (9H, s), 1.67 (1H, m), 2.37 (2H, d), 2.65 (2H, d), 2.77 (1H, m), 2.85 (1H, dd), 3.41 (1H, m), 3.72 (2H, m), 4.63 (1H, d), 5.15 (2H, s), 6.89 (2H, d), 7.12 (2H, d), 7.19 (1H, dd), 7.49 (1H, d), 7.67 (1H, t), 8.57 (1H, d).

Step 4:

***t*-Butyl-N((1*S*,2*R*)-1-(4-(2-pyridylmethoxy)benzyl)-3-*i*-butyl-[(3-nitrobenzene)sulfonyl]-amino-2-hydroxypropyl-carbamate**



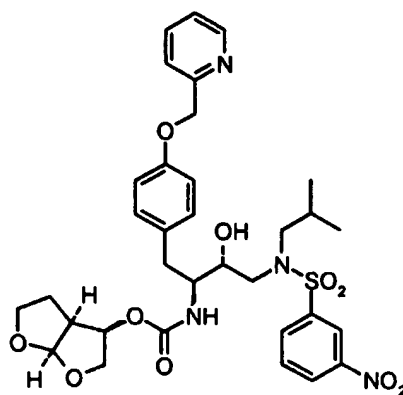
5

A CH₂Cl₂ (10 mL) solution of t-Butyl-(1S,2R)-1-(4-(2-pyridylmethoxy)benzyl)-3-*i*-butylamino-2-hydroxypropyl-carbamate (320 mg, 0.72 mmol), 3-nitrobenzenesulfonyl chloride (200 mg, 0.90 mmol), and diisopropylethylamine (186 mg, 1.44 mmol) was stirred at 20°C for 12 hours. Water (20 mL) was then added to the reaction mixture and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (3x25 mL). The combined organic phases were dried over MgSO₄ and concentrated. The residue was then filtered through SiO₂ using CH₂Cl₂-acetone (3:2) as eluent. The filtrate was concentrated under reduced pressure to yield title product (330 mg, 75%).

¹H NMR (DMSO-d₆): δ 0.78 (6H, d), 1.20 (9H, s), 1.93 (1H, m), 2.37 (1H, dd), 2.85 (1H, dd), 3.10 (2H, m), 3.42 (1H, d), 4.88 (1H, d), 5.08 (2H, s), 6.61 (1H, d), 6.85 (2H, d), 7.04 (2H, d), 7.29 (1H, m), 7.44 (1H, d), 7.82 (2H, m), 8.19 (1H, d), 8.43 (2H, s), 8.53 (1H, d).

5 Step 5:

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-(2-pyridylmethoxy)benzyl)-3-i-butyl-[(3-nitrobenzene)sulfonyl]-amino-2-hydroxypropyl)-carbamate



10

Trifluoroacetic acid (4 mL) was added dropwise to a solution of t-Butyl-N((1S,2R)-1-(4-(2-pyridylmethoxy)benzyl)-3-i-butyl-[(3-nitrobenzene)sulfonyl]-amino-2-hydroxypropyl)-carbamate (330 mg, 0.52 mmol) in CH₂Cl₂ (8 mL). The mixture was stirred at 20°C for 1.5 hour, then concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (50 mL) and 10% aqueous Na₂CO₃ solution (50 mL) was added. The mixture was stirred at 20°C for 15 minutes. Phases were separated, and the aqueous phase was extracted with additional CH₂Cl₂ (2x50 ml). The combined organic phases were then dried over Na₂CO₃ and concentrated under reduced

-170-

pressure. The residue was dissolved in acetonitrile (7 mL). Diisopropylethylamine (269 mg, 2.08 mmol) and (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl-4-nitrophenyl carbonate (272 mg, 0.92 mmol) were added, and the solution was stirred at 20°C for 12 hours. Then, 25% aqueous ammonium hydroxide solution (2 mL) was added, and the mixture was stirred for an additional 0.5 hour. The solvents were removed under reduced pressure. The residue was dissolved in EtOAc (50 mL), and the solution was extracted with 5% aqueous Na₂CO₃ solution (10x25 mL) and washed with brine (1x75 mL). The organic phase was dried over Na₂CO₃, and concentrated in vacuo. The residue was chromatographed on SiO₂ using EtOAc as eluent to afford title compound (175 mg, 50%).

15

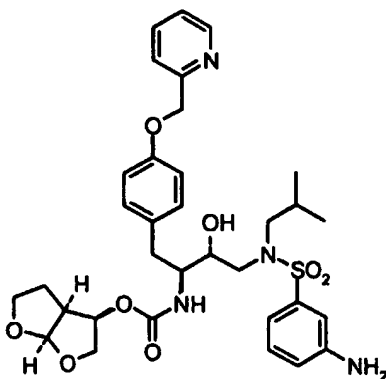
¹H NMR (DMSO-d₆): δ 0.78 (3H, d), 0.82 (3H, d), 1.21 (1H, m), 1.33 (1H, m), 1.92 (1H, m), 2.35 (1H, dd), 2.73 (1H, m), 2.85 (2H, m), 3.05 (1H, m), 3.12 (1H, m), 3.45 (1H, m), 3.52 (1H, m), 3.64 (1H, t), 3.78 (1H, dd), 4.81 (1H, q), 4.97 (1H, d), 5.06 (2H, s), 5.46 (1H, d), 6.85 (2H, d), 7.05 (2H, d), 7.17 (1H, d), 7.29 (1H, dd), 7.44 (1H, d), 7.78 (1H, t), 7.84 (1H, t), 8.19 (1H, d), 8.42 (2H, m), 8.53 (1H, d): MS: 685 (M⁺).

25 Step 6:

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-(2-pyridylmethoxy)benzyl)-3-*i*-butyl-[(3-aminobenzene)sulfonyl]-amino-2-hydroxypropyl-carbamate (293)

30

-171-



(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-(2-pyridylmethoxy)benzyl)-3-i-butyl-[(3-nitrobenzene)sulfonyl]-amino-2-hydroxypropyl)-carbamate (170 mg, 0.25 mmol) in THF (7 mL) was added Pt/C (3% Pt) (100 mg). The mixture was hydrogenated under atmospheric pressure H₂ for 12 hours. The catalyst was removed by filtration through Celite, and the solvent was evaporated in vacuo. The residue was chromatographed on SiO₂ using EtAOc as eluent to yield title compound (75 mg, 46%).

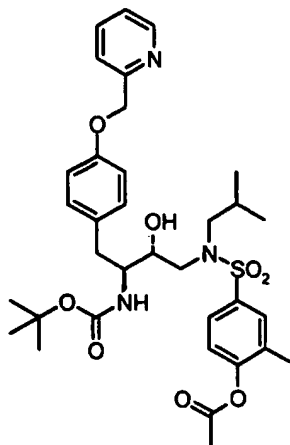
¹H NMR (DMSO-d₆): δ 0.78 (3H, d), 0.82 (3H, d), 1.21 (1H, m), 1.30 (1H, m), 1.93 (1H, m), 2.36 (1H, t), 2.72 (3H, m), 2.97 (2H, m), 3.55 (4H, m), 3.65 (1H, t), 3.79 (1H, dd), 4.80 (1H, m), 4.95 (1H, d), 5.06 (2H, s), 5.45 (1H, d), 5.53 (2H, broad s), 6.72 (1H, d), 6.79 (1H, d), 6.83 (2H, d), 6.91 (1H, s), 7.08 (2H, d), 7.13 (1H, t), 7.17 (1H, d), 7.28 (1H, d), 7.45 (1H, d), 7.77 (1H, t), 8.53 (1H, d); MS: 655 (M⁺).

Example 83

25 Step 1:

-172-

***t*-Butyl-N((1*S*,2*R*)-1-(4-(2-pyridylmethoxy)benzyl)-3-*i*-butyl-[(3-methyl-4-acetoxy)benzenesulfonyl]-amino-2-hydroxypropyl-carbamate**



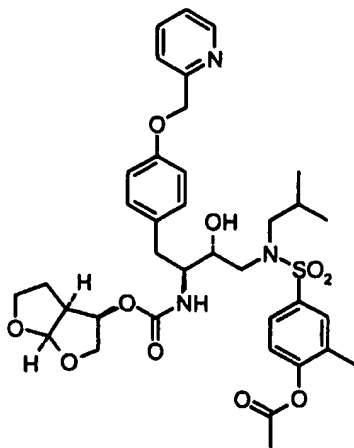
5 A CH₂Cl₂ (15 mL) solution of *t*-Butyl-(1*S*,2*R*)-1-(4-(2-pyridylmethoxy)benzyl)-3-*i*-butylamino-2-hydroxypropyl-carbamate (630 mg, 1.42 mmol) was added (3-methyl-4-acetoxy)benzenesulfonyl chloride (442 mg, 1.78 mmol), and diisopropylethylamine (367 mg, 2.84 mmol). The mixture
10 was stirred at room temperature for 1 hour, and concentrated. The residue was added water (50 mL), and stirred at 20°C for 30 minutes to afford title compound (675 mg, 75%).

15 MS: 656 (M⁺).

Step 2:

(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-yl-N((1*S*,2*R*)-1-(4-(2-pyridylmethoxy)benzyl)-3-*i*-butyl-[(3-methyl-4-acetoxy)benzenesulfonyl]-amino-2-hydroxypropyl-carbamate
20 (294)

-173-



A CH_2Cl_2 (15 mL) and TFA (7.5 mL) solution of t-Butyl-N((1S,2R)-1-(4-(2-pyridylmethoxy)benzyl)-3-i-butyl-[(3-methyl-4-acetoxy)benzenesulfonyl]-amino-2-hydroxypropyl)-carbamate (650 mg, 1 mmol) was stirred at 20°C for 1 hour, and concentrated. The residue was dissolved in EtOAc (50 mL), and washed with 2% aqueous NaHCO_3 solution (3x25 mL). The organic phase was dried over MgSO_4 , and filtered.

Diisopropylethylamine (517 mg, 4 mmol) and (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl-4-nitrophenyl carbonate (517 mg, 1.75 mmol) were then added, and the solvent was evaporated. The residue was dissolved in CH_3CN (20 mL), and more diisopropylethylamine (517 mg, 4 mmol) was added. The resulting solution was stirred at room temperature for 3 hours, and concentrated. The residue was dissolved in EtOAc (150 mL), then washed with water (1x100 mL), 5% aqueous Na_2CO_3 (10x100 mL), and brine (1x100 mL). The organic phase was dried over MgSO_4 , filtered, and concentrated. The residue was then chromatographed on SiO_2 using EtOAc as eluent to yield title compound (385 mg, 55%).

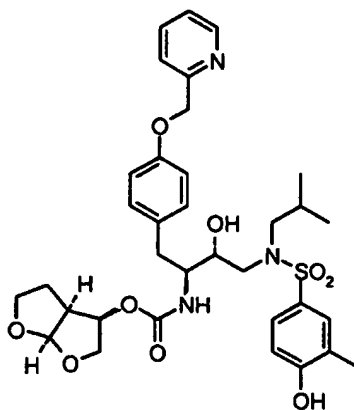
-174-

¹H NMR (DMSO-d₆): δ 0.78 (3H, d), 0.82 (3H, d), 1.20 (1H, m), 1.35 (1H, m), 2.17 (3H, s), 2.30 (3H, s), 2.37 (1H, t), 2.76 (3H, m), 2.91 (1H, d), 3.04 (1H, dd), 3.56 (4H, m), 3.66 (1H, t), 3.79 (1H, dd), 4.80 (1H, dd), 5.01 (1H, d), 5.07 (2H, s), 5.46 (1H, d), 6.85 (2H, d), 7.09 (2H, d), 7.19 (1H, d), 7.26 (1H, d), 7.30 (2H, t), 7.46 (1H, d), 7.61 (1H, d), 7.70 (1H, s), 7.78 (1H, t), 8.53 (1H, d); MS: 712 (M⁺).

10

Example 84

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-(2-pyridylmethyloxy)benzyl)-3-*i*-butyl-[(3-methyl-4-hydroxy)benzenesulfonyl]-amino-2-hydroxypropyl-carbamate (295)



(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-(2-pyridylmethyloxy)benzyl)-3-*i*-butyl-[(3-methyl-4-acetoxy)benzenesulfonyl]-amino-2-hydroxypropyl-carbamate (180 mg, 0.25 mmol) was dissolved in MeOH (3 mL), and K₂CO₃ (30 mg) was added. The mixture was stirred at room temperature for 30 minutes, diluted with EtOAc (50 mL), and washed with water (3x50 mL). The organic phase was

20

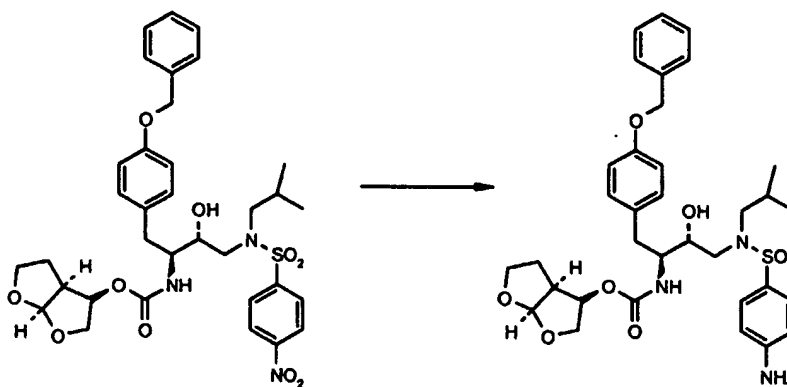
-175-

dried over MgSO_4 , concentrated, and dried in vacuo to yield title compound (115 mg, 70%).

^1H NMR ($\text{DMSO}-d_6$): δ 0.78 (3H, d), 0.82 (3H, d), 1.18 (1H, m), 1.27 (1H, m), 1.90 (1H, m), 2.37 (1H, t), 2.65 (3H, m), 2.91 (2H, m), 3.52 (4H, m), 3.65 (1H, t), 3.80 (1H, dd), 4.79 (1H, dd), 5.06 (2H, s), 5.46 (1H, d), 6.84 (3H, m), 7.07 (2H, d), 7.18 (1H, d), 7.30 (1H, dd), 7.38 (1H, d), 7.45 (2H, d), 7.78 (1H, d), 8.52 (1H, d), 10.31 (1H, s); MS: 670 (M^+).

Example 85

(3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
[[4-(4-aminophenyl)sulfonyl](isobutyl)amino]-1-[4-(benzyloxy)benzyl]-2-hydroxypropylcarbamate (296)



To a stirred solution of (3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-{isobutyl[(4-nitrophenyl)sulfonyl]amino}propylcarbamate (0.20 g, 0.29 mmol) in 3 mL of ethanol was added 64 mg of platinum (on activated carbon, 3% Pt). The mixture was stirred under an atmospheric pressure of hydrogen for 12

-176-

hours. The catalyst was filtered, and the solvent was removed under reduced pressure. The residue was purified on silica gel using ethyl acetate-hexanes (4:1) as eluent to provide 0.10 g (52%) of the title compound.

5

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 0.74 (3H,d), 0.81 (3H,d), 1.19 (1H,m), 1.29 (1H,m), 1.89 (1H, m), 2.34 (1H,t), 2.54-2.62 (2H,m), 2.71 (1H,m), 2.90 (2H,m), 3.22 (1H,d), 3.46 (1H,m), 3.52-3.59 (3H,m), 3.66 (1H,t) 3.83 (1H,dd), 4.80 (1H,q), 4.92 (1H,d,b), 4.99 (2H,s), 5.47 (1H,d), 5.94 (2H,s), 6.54 (2H,d), 6.81 (2H,d), 7.07 (2H,d), 7.19 (1H,d), 7.28 (1H,d), 7.35 (5H,m). MS: 655 (M^+).

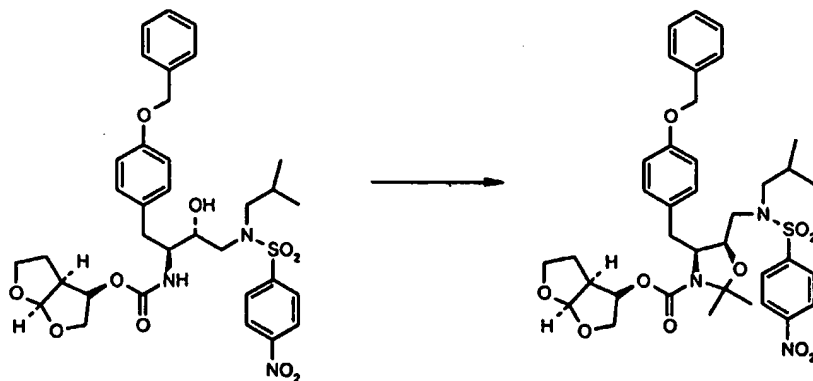
10

Example 86

15 Step 1:

(3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-4-[4-(benzyloxy)benzyl]-5-({isobutyl[(4-nitrophenyl)sulfonyl]amino}methyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate.

20



To a solution of (3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-

25

-177-

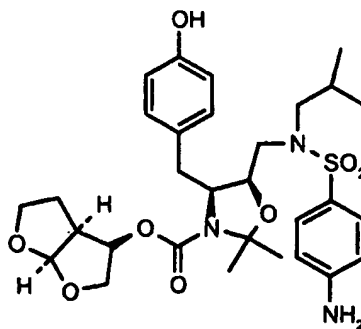
{isobutyl[(4-nitrophenyl)sulfonyl]amino}propylcarbamate (1.00 g, 1.5 mmol) in 20 mL of dichloromethane was added 2,2-dimethoxypropane (1.5 g, 14.6 mmol) and *p*-toluenesulfonic acid (0.09 g, 0.5 mmol). The solution
5 was refluxed for 12 hours, and the solvent was removed under reduced pressure. The residue was purified on silica gel using ethyl acetate-hexanes (3.5:6.5) as eluent to provide 0.70 g (70%) of the title compound.

10 ¹H-NMR (CDCl₃): δ 0.85 (3H,d), 0.90 (3H,d), 1.35,1.44 (3H,s)*, 1.55,1.61 (3H,s)*, 1.84-2.00 (3H,m,b), 2.61-2.91 (4H,m), 2.91-3.08 (3H,m), 3.17,3.33 (1H,d)*, 3.56 (1H,t), 3.80-3.86 (2H,m), 3.91-3.98 (1H,m), 4.23-4.27 (2H, m), 5.02-5.16 (2H,s), 5.67 (1H,d), 6.91 (2H,d), 7.03 (1H,d),
15 7.14 (1H,d), 7.31 (1H,d), 7.38 (2H,m), 7.45 (2H,d), 7.67 (2H,d), 8.25 (2H,d).

*possible indication for rotamers.

20 Step 2:
(3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-{[[[(4-aminophenyl)sulfonyl](isobutyl)amino]methyl]-4-(4-hydroxybenzyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate.

25



-178-

To a stirred solution of (3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-4-[4-(benzyloxy)benzyl]-5-
(({isobutyl[(4-nitrophenyl)sulfonyl]amino)methyl})-2,2-
dimethyl-1,3-oxazolidine-3-carboxylate. (0.18 g, 0.25
5 mmol) in 6 mL of a 2M solution of ammonia in methanol was
added 0.18 g of palladium (on charcoal, 10% Pd, Degussa
type). The mixture was stirred under an atmospheric
pressure of hydrogen for 12 hours. The catalyst was
filtered, and the solvent was removed under reduced
10 pressure. The residue was purified on silica gel using
ethyl acetate-hexanes (7:3) as eluent to provide 81 mg
(54%) of the title compound.

¹H-NMR (DMSO-*d*₆): δ 0.76 (3H,d), 0.80 (3H,d), 1.19,1.33
15 (3H,s)*, 1.44, 1.50 (3H,s)*, 1.74 (2H,m), 1.89 (1H,m),
2.49-2.75 (6H,m), 2.89-2.99 (2H,m), 3.19 (1H,m), 3.61
(2H,m), 3.80 (1H,m), 4.07 (1H,m), 4.74 (1H,q), 5.50,5.54
(1H,d)*, 5.94 (2H,s,b), 6.54 (2H,d), 6.64 (2H,d),
6.93,6.99 (2H,d)*, 7.13,7.20 (2H,d)*, 9.20, 9.22 (1H,s)*.
20 MS: 605 (M⁺).

*possible indication for rotamers.

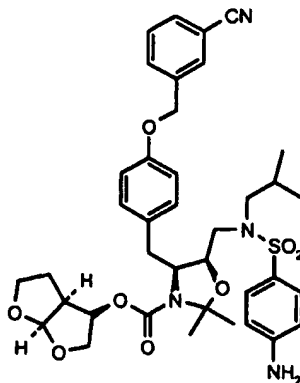
Step 3:

25

(3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
{[[[4-aminophenyl)sulfonyl](isobutyl)amino]methyl}-4-{4-
[(3-cyanobenzyl)oxy]benzyl}-2,2-dimethyl-1,3-oxazolidine-
3-carboxylate.

30

-179-



To a stirred mixture of (3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-
 b]furan-3-yl (4*S*,5*R*)-5-[[[(4-
 5 aminophenyl)sulfonyl](isobutyl)amino]methyl]-4-(4-
 hydroxybenzyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate
 (40 mg, 0.07 mmol) and cesium carbonate (22 mg, 0.07
 mmol) in 1.5 mL of *N,N*-dimethylformamide was added 3-
 bromomethylbenzonitrile (13 mg, 0.07 mmol). The mixture
 10 was stirred at room temperature for 12 hours followed by
 dilution with 25 mL of ether. The ether was extracted
 with water (5 x 15 mL). The organic phase was dried with
 magnesium sulfate, filtered, and concentrated under
 reduced pressure. The residue was purified on silica gel
 15 using ethyl acetate-hexanes (8.5:1.5) as eluent to
 provide 41 mg (85%) of the title compound.

¹H-NMR (DMSO-*d*₆): δ 0.80-0.86 (6H,dd), 1.37 (3H,s),
 1.48,1.55 (3H,s)*, 1.75 (2H,m), 1.94 (1H,m), 2.58-2.78
 20 (6H,m), 2.92-3.09 (2H,m), 3.15-3.21 (1H,m), 3.61 (2H,m),
 3.81 (1H,m), 4.14 (1H,m), 4.74 (1H,q), 5.17 (2H,s),
 5.53,5.57 (1H,d)*, 5.99 (2H,s,b), 6.58 (2H,d), 6.95
 (2H,d), 7.11,7.14 (2H,d)*, 7.22,7.28 (2H,d)*, 7.60
 (1H,t), 7.80 (2H,m,b), 7.91 (1H,s).

-180-

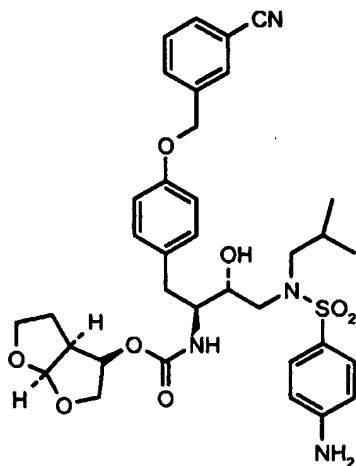
*possible indication for rotamers.

Step 4:

5

(3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
[[(4-aminophenyl)sulfonyl] (isobutyl) amino] -1-{4-[(3-
cyanobenzyl)oxy]benzyl}-2-hydroxypropylcarbamate (301)

10



To a stirred solution of (3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-
b]furan-3-yl (4*S*,5*R*)-5-[[(4-
15 aminophenyl)sulfonyl] (isobutyl) amino]methyl}-4-{4-[(3-
cyanobenzyl)oxy]benzyl}-2,2-dimethyl-1,3-oxazolidine-3-
carboxylate in 3 mL of dioxane was added 4M hydrochloric
acid in dioxane (1.5 mL) and water (0.05 mL). The
solution was stirred for 1 hour followed by
20 neutralization with 10% aqueous Na₂CO₃. The solution was
extracted with dichloromethane (3 x 15 mL). The organic
phase was dried with magnesium sulfate, filtered, and
concentrated under reduced pressure. The residue was

-181-

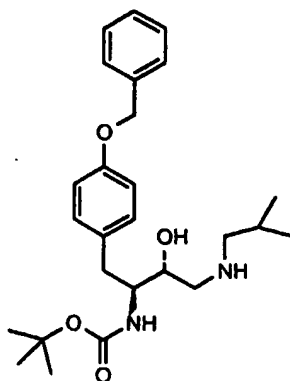
purified on silica gel using ethyl acetate-hexanes (8:2) as eluent to provide 17 mg (61%) of the title compound.

¹H-NMR (DMSO-*d*₆): δ 0.74 (3H,d), 0.81(3H,d), 1.18
5 (1H,m), 1.28 (1H,m), 1.89 (1H,m), 2.35 (1H,t), 2.54-2.60
(2H,m), 2.71 (1H,m), 2.86-2.93 (2H,m), 3.22-3.29 (1H,dd),
3.42-3.48 (1H,m), 3.53-3.59 (3H,m), 3.65 (1H,t), 3.82
(1H,q), 4.80 (1H,q), 4.93 (1H,d,b), 5.07 (2H,s), 5.47
(1H,d), 5.94 (2H,s,b), 6.54 (2H,d), 6.83 (2H,d), 7.08
10 (2H,d), 7.19 (1H,d), 7.33 (2H,d), 7.56 (1H,t), 7.74
(2H,t), 7.85 (1H,s). MS: 680 (M⁺).

Example 81

15 Step 1:

tert-butyl (1*S*,2*R*)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(*isobutylamino*)propylcarbamate.



20

To a solution of *t*-Butyl-(1*S*,2*R*)-1-(4-benzyloxy-benzyl)-2,3-epoxydo-propyl-carbamate (3.2 g, 8.7 mmol) in 50 mL of *i*-propanol was added *i*-butylamine (4.6 g, 62.4 mmol). The mixture was stirred at 85°C for 2 hours, and then it

-182-

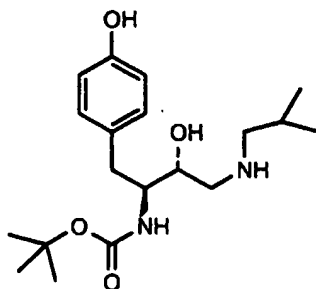
was cooled to 5°C followed by dropwise addition into 250 mL of water. The resulting suspension was stirred for 30 minutes at 5°C and then filtered. The solid was washed with water (3 x 150 mL) and dried under reduced pressure
5 to yield 2.4 g (61%) of the title compound.

¹H-NMR (CDCl₃): δ 0.91 (6H,d), 1.34 (9H,s), 1.77 (1H,m),
2.37-2.48 (2H,m), 2.66-2.75 (2H,m), 2.82-2.93 (2H,m),
3.42 (1H,m), 3.77 (1H,m), 4.64 (1H,d), 5.01 (2H,s), 6.89
10 (2H,d), 7.12 (2H,d), 7.27-7.31 (1H,m), 7.34-7.41 (4H,m).

Step 2:

tert-butyl (1*S*,2*R*)-2-hydroxy-1-(4-hydroxybenzyl)-3-(isobutylamino)propylcarbamate.

15



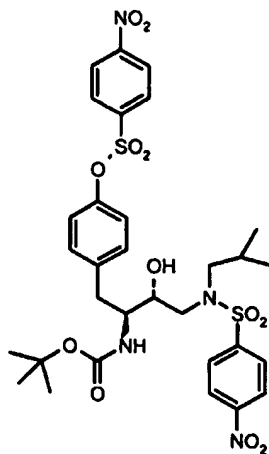
To a stirred solution of *tert*-butyl (1*S*,2*R*)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-(isobutylamino)
20 propylcarbamate (0.5 g, 1.1 mmol) in anhydrous tetrahydrofuran (12 mL) was added 0.5 g of palladium (on charcoal, 10% Pd, Degussa type). The mixture was stirred under an atmospheric pressure of hydrogen for 12 hours. The catalyst was filtered and the solvent was removed
25 under reduced pressure resulting in 0.4 g (98%) of the title compound.

-183-

¹H-NMR (CDCl₃): δ 0.92 (6H,dd), 1.35 (9H,s), 1.83 (1H,m), 2.44-2.55 (2H,m), 2.73-2.85 (4H,m), 3.49 (1H,m), 3.70-3.79 (1H,m,b), 4.66 (1H,d), 6.72 (2H,d), 7.05 (2H,d).

Step 3:

4-((2*S*,3*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-4-{isobutyl[(4-nitrophenyl)sulfonyl]-amino}butyl)phenyl 4-nitrobenzenesulfonate



15

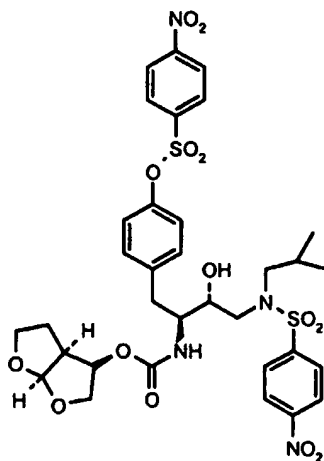
To a solution of *tert*-butyl (1*S*,2*R*)-2-hydroxy-1-(4-hydroxybenzyl)-3-(isobutylamino)propylcarbamate (50 mg, 0.14 mmol) in 3 mL of anhydrous dichloromethane were added 4-nitrobenzenesulfonyl chloride (38 mg, 0.17 mmol) and *N*-ethyldiisopropylamine (74 mg, 0.57 mmol). After 2 hours, the solvent was removed under reduced pressure. The residue was purified on silica gel using ethyl

acetate-hexanes (2:3) as eluent to provide 66 mg (87%) of the title compound.

¹H-NMR (DMSO-d₆): δ 0.77, 0.79 (6H, dd), 1.17 (9H, s),
5 1.91 (1H, m), 2.36-2.43 (1H, m), 2.84-2.95 (2H, m), 2.97-
3.01 (2H, m), 3.07-3.12 (2H, m), 3.39-3.47 (1H, m), 4.95
(1H, d), 6.67 (1H, d), 6.91 (2H, d), 7.13 (2H, d), 8.00
(2H, d), 8.07 (2H, d), 8.32 (2H, d), 8.38 (2H, d).

10 Step 4:

4-((2*S*,3*R*)-2-({[(3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-
yloxy]carbonyl}amino)-3-hydroxy-4-{isobutyl[(4-
nitrophenyl)sulfonyl]amino}butyl)phenyl 4-
15 nitrobenzenesulfonate (297)



To a solution of 4-((2*S*,3*R*)-2-[(*tert*-
20 butoxycarbonyl)amino]-3-hydroxy-4-{isobutyl[(4-
nitrophenyl)sulfonyl]-amino}butyl)phenyl 4-
nitrobenzenesulfonate (0.21 mg, 0.29 mmol) in 10 mL of
dichloromethane was added dropwise trifluoroacetic acid

-185-

(2 mL). The mixture was stirred for 1 hour at room temperature. The solvents were removed under reduced pressure; the residue was redissolved in 50 mL of dichloromethane and 20 mL of 5% aqueous sodium carbonate was added. The aqueous phase was separated and extracted with dichloromethane (2 x 20 mL). The combined organic phases were dried over sodium carbonate, filtered, and concentrated under reduced pressure. The residue was redissolved in 10 mL of acetonitrile. N-Ethyl-diisopropylamine (80 uL, 0.05 mmol) and (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl-4-nitrophenylcarbonate (0.11g, 0.37 mmol) were added, and the solution was stirred for 12 hours. The solvents were removed under reduced pressure. The residue was redissolved in ethyl acetate (30 mL), and the organic phase was extracted with water (20 mL) followed by 5% aqueous sodium carbonate solution (5 x 20 mL). The organic phase was dried with sodium carbonate, filtered, and concentrated under reduced pressure. The residue was purified on silica gel using ethyl acetate-hexanes as eluent to provide 0.12 g (55%) of the title compound.

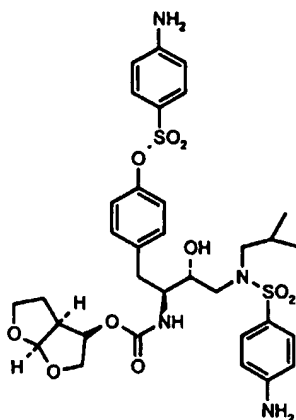
$^1\text{H-NMR}$ (CD_3OD): δ 0.84 (3H,d), 0.90 (3H,d), 1.46 (1H,m), 1.58 (1H,m), 1.99 (1H,m), 2.47 (1H,t), 2.87-2.97 (2H,m), 3.04-3.10 (2H,m), 3.18 (1H,m), 3.44-3.47 (1H,dd), 3.62-3.68 (4H,m), 3.79 (1H,m), 3.89 (1H,q), 4.91 (1H,q), 5.57 (1H,d), 6.91 (2H,d), 7.20 (2H,d), 8.02-8.05 (4H,d+d), 8.36-8.42 (4H,d+d). MS: 778 (M^+).

30

Example 82

-186-

(3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(4-aminobenzyl)(isobutyl)amino]-1-{4-[(4-
 aminobenzyl)oxy]benzyl}-2-hydroxypropylcarbamate (298)



5

To a stirred solution of 4-((2*S*,3*R*)-2-({[(3*S*,3*aS*,6*aR*)-
 hexahydrofuro[2,3-*b*]furan-3-yloxy]carbonyl}amino)-3-
 hydroxy-4-{isobutyl[(4-
 10 nitrophenyl)sulfonyl]amino}butyl)phenyl 4-
 nitrobenzenesulfonate (0.12 g, 0.15 mmol) in 2 mL of
 anhydrous tetrahydrofuran was added 36 mg of platinum (on
 activated carbon, 3% Pt). The mixture was stirred under
 an atmospheric pressure of hydrogen for 3 hours. The
 15 catalyst was filtered, and the solvent was removed under
 reduced pressure. The residue was purified on silica gel
 using ethyl acetate-hexanes (9:1) as eluent to provide 39
 mg (35%) of the title compound.

20 ¹H-NMR (CD₃OD): δ 0.84 (3H,d), 0.90 (3H,d), 1.38-1.43
 (1H,m), 1.53-1.59 (1H,m), 1.96 (1H,m), 2.47 (1H,t), 2.70-
 2.88 (4H,m), 2.98 (1H,m), 3.13,3.21 (1H,dd), 3.31,3.35
 (1H,dd), 3.64-3.71 (4H,m), 3.73-3.82 (3H,m), 3.85-3.92
 (1H,m), 4.91 (1H,q), 5.57 (1H,d), 6.62,6.66 (4H,d+d),

-187-

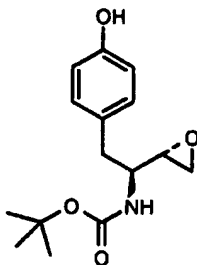
6.82 (2H,d), 7.16 (2H,d), 7.38 (2H,d), 7.45 (2H,d). MS:
720 (M⁺).

5

Example 83

Step 1:

tert-butyl (1S)-2-(4-hydroxyphenyl)-1-[(2S)-
oxiranyl]ethylcarbamate.



10

To a stirred solution of t-Butyl-(1S,2R)-1-(4-benzyloxy-
benzyl)2,3-epoxydo-propylcarbamate in a mixture of
ethanol-ethyl acetate (4:1) was added palladium hydroxide
15 (on carbon, 20% palladium). The mixture was stirred under
an atmospheric pressure of hydrogen for 2 hours. The
catalyst was filtered and washed one time each with
ethanol, methanol, and ethyl acetate. The solvent was
removed under reduced pressure providing 0.5 g
20 (quantitative) of the title compound.

¹H-NMR (DMSO-d₆): δ 1.30 (9H,s), 2.59-2.75 (4H,m), 2.85
(1H,m), 3.35-3.46 (1H,m), 6.63 (2H,d), 6.78 (1H,d), 6.98
(2H,d), 9.03,9.12 (1H,s)*.

25

*possible indication for rotamers.

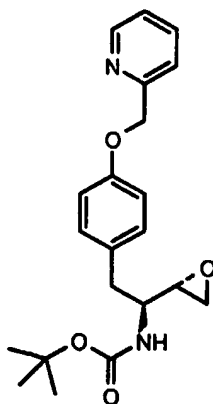
Step 2:

General procedure for the alkylation of product from Procedure 11.

5

To a stirred mixture of *tert*-butyl (1*S*)-2-(4-hydroxyphenyl)-1-[(2*S*)-oxiranyl]ethylcarbamate (0.25 g, 0.90 mmol) and cesium carbonate (0.73 g, 2.2 mmol) in 5 mL of *N,N*-dimethylformamide was added the desired alkyl
10 halide [1] (0.90 mmol). The mixture was stirred at room temperature for 12 hours followed by dilution with 125 mL of ether. The ether was extracted with water (5 x 75 mL). The organic phase was dried with magnesium sulfate, filtered, and concentrated under reduced pressure. The
15 residue was purified on silica gel using ethyl acetate-hexanes [2] as eluent to provide the following compounds [Y:(3)]:

1. *tert*-butyl (1*S*)-1-[(2*S*)-oxiranyl]-2-[4-(2-pyridinylmethoxy)phenyl]ethylcarbamate.
20



[1]: 2-Picolyl chloride hydrochloride; [2]: no purification; [3]: 91%.

25

-189-

^1H -NMR (DMSO- d_6): δ 1.23 (9H,s), 2.56-2.63 (3H,m), 2.71-2.76 (1H,m), 2.85 (1H,m), 3.40 (1H,m), 5.08 (2H,s), 6.79 (1H,d), 6.87 (2H,d), 7.07 (2H,d), 7.29 (1H,m), 7.44 (1H,d), 7.77 (1H,t), 8.52 (1H,d).

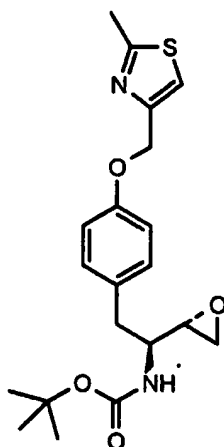
5

Example 84

Step 1

2. *tert*-butyl (1*S*)-2-{4-[(2-methyl-1,3-thiazol-4-yl)methoxy]phenyl}-1-[(2*S*)-oxiranyl]-ethylcarbamate.

10



[1]: 4-Chloromethyl-2-methylthiazole hydrochloride*;
15 [2]: (6:4); [3]: 35%.

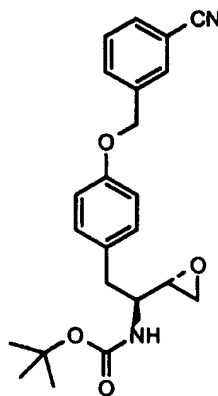
^1H -NMR (DMSO- d_6): δ 1.24 (9H,s), 2.57-2.63 (6H,m+s),
2.72, 2.76 (1H, dd), 2.84 (1H,m), 3.41 (1H,m), 5.00
(2H,s), 6.79 (1H,d), 6.87 (2H,d), 7.07 (2H,d), 7.46
20 (1H,s).

*added excess sodium iodide to the reaction.

Example 85

5 Step 1:

3. *tert*-butyl (1*S*)-2-{4-[(3-cyanobenzyl)oxy]phenyl}-1-[(2*S*)-oxiranyl]ethylcarbamate.



10

[1]: 3-(Bromomethyl)benzonitrile; [2]: (1:1); [3]:
75%.

15 ¹H-NMR (DMSO-*d*₆): δ 1.23 (9H,s), 2.55-2.63 (3H,m),
2.72,2.75 (1H,dd), 2.84 (1H,m), 3.41 (1H,m), 5.09 (2H,s),
6.79 (1H,d), 6.88 (2H,d), 7.08 (2H,d), 7.56 (1H,t), 7.74
(2H,t), 7.84 (1H,s).

20

Example 83, Step 3:

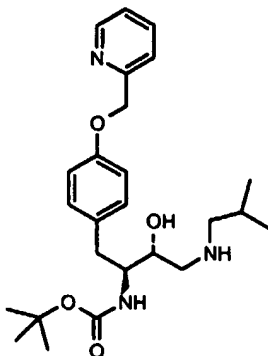
General procedure for the ring-opening

To a solution of the product from the previous step (0.4
25 g, 1.2 mmol) in *i*-propanol was added *i*-butylamine (0.4 g,

-191-

5.8 mmol). The mixture was stirred at 85°C for 2 hours, and then it was cooled to 5°C followed by dropwise addition into 50 mL of water. The resulting suspension was stirred for 30 minutes at 5°C and then filtered. The solid was washed with water (3 x 25 mL) and dried under reduced pressure to provide the following compounds [Y: (1)]:

1. *tert*-butyl (1*S*,2*R*)-2-hydroxy-3-(isobutylamino)-1-[4-(2-pyridinylmethoxy)benzyl]-propylcarbamate.



[1]: 82%.

15

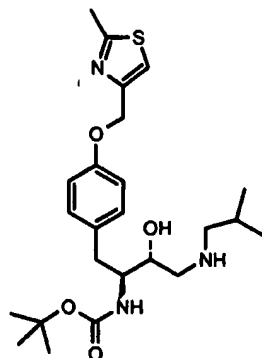
¹H-NMR (DMSO-*d*₆): δ 0.82 (6H,dd), 1.21 (9H,s), 1.59 (1H,m), 2.25 (2H,d), 2.39-2.42 (2H,m), 2.51 (1H,m), 2.85 (1H,dd), 3.34-3.43 (3H,m), 4.71 (1H,s,b), 5.08 (2H,s), 6.65 (1H,d), 6.85 (2H,d), 7.04 (2H,d), 7.29 (1H,m), 7.43 (1H,d), 7.77 (1H,t), 8.52 (1H,d).

20

Example 84, Step 2:

-192-

tert-butyl (1*S*,2*R*)-2-hydroxy-3-(isobutylamino)-1-{4-[(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl}propylcarbamate.



5

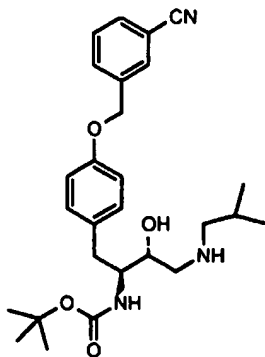
[1]: 66%.

¹H-NMR (DMSO-*d*₆): δ 0.81 (6H,d), 1.22 (9H,s), 1.60 (1H,m), 2.27 (2H,m), 2.40-2.55 (2H,m,b), 2.60 (3H,s),
 10 2.86 (1H,d,b), 3.35-3.42 (3H,m), 4.73 (1H,s,b), 4.99 (2H,s), 6.65 (1H,d), 6.85 (2H,d), 7.03 (2H,d), 7.45 (1H,s).

Example 85, Step 2:

15

tert-butyl (1*S*,2*R*)-1-{4-[(3-cyanobenzyl)oxy]benzyl}-2-hydroxy-3-(isobutylamino)-propylcarbamate.



[1]: 88%.

¹H-NMR (DMSO-d₆): δ 0.80 (6H,d), 1.21 (9H,s), 1.59
5 (1H,m), 2.25 (2H,d), 2.43 (2H,m), 2.51 (1H,m), 2.86
(1H,dd), 3.34 (1H,m), 3.41 (1H,m), 4.70 (1H,s,b), 5.07
(2H,s), 6.64 (1H,d), 6.85 (2H,d), 7.04 (2H,d), 7.55
(1H,t), 7.74 (2H,t), 7.84 (1H,s).

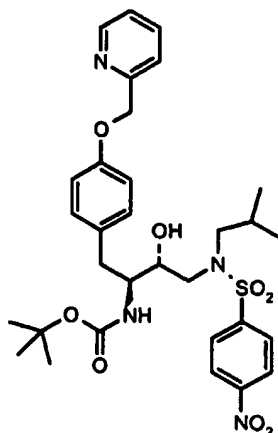
10 **Example 83, Step 4:**

General procedure for the sulfonylation

To a stirred solution of the product from the previous
step (0.42 g, 0.96 mmol) in 20 mL of anhydrous
15 dichloromethane were added 4-nitrobenzenesulfonyl
chloride (0.25 g, 1.1 mmol) and N-ethyldiisopropylamine
(0.15 g, 1.7 mmol). The mixture was allowed to react for
the given number of hours [1] and at which time the
solvent was removed under reduced pressure. The residue
20 was redissolved in dichloromethane and extracted with
water (3 x 50 mL). The organic phase was dried with
magnesium sulfate, filtered, and removed under reduced
pressure. The residue was purified on silica gel using
ethyl acetate-hexanes [2] as eluent to provide the
25 following compounds [Y:(3)]:

1. tert-butyl (1S,2R)-2-hydroxy-3-{isobutyl[(4-
nitrophenyl)sulfonyl]amino}-1-[4-(2-
pyridinylmethoxy)benzyl]propylcarbamate.

-194-



[1]: 6 hours; [2]: (7:3); [3]: 87%.

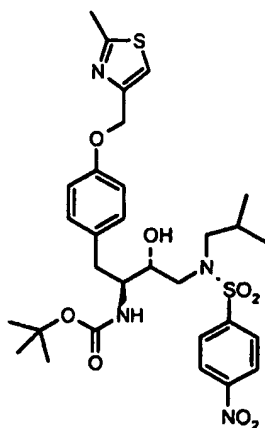
5 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 0.77, 0.80 (6H, dd), 1.20 (9H, s), 1.92 (1H, m), 2.36 (2H, d), 2.80-2.91 (2H, m), 2.98-3.13 (2H, m), 3.42-3.46 (2H, m), 4.89 (1H, d), 5.07 (2H, s), 6.61 (1H, d), 6.84 (2H, d), 7.03 (2H, d), 7.29 (1H, m), 7.43 (1H, d), 7.76 (1H, m), 8.00 (2H, d), 8.32 (2H, d), 8.52 (1H, d).

10

Example 84, Step 3:

tert-butyl (1S,2R)-2-hydroxy-3-{isobutyl[(4-nitrophenyl)sulfonyl]amino}-1-{4-[(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl}propylcarbamate.

15



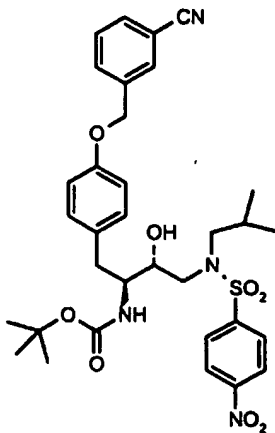
[1]: 12 hours; [2]: (1:1); [3]: 83%.

¹H-NMR (DMSO-d₆): δ 0.79 (6H,dd), 1.21 (9H,s), 1.93
5 (1H,m), 2.34-2.40 (2H,m), 2.60 (3H,s), 2.80-2.91 (2H,m),
2.99-3.13 (2H,m), 3.33 (1H,m), 3.44 (1H,m), 4.89 (1H,d),
4.99 (2H,s), 6.63 (1H,d), 6.85 (2H,d), 7.04 (2H,d), 7.45
(1H,s), 8.01 (2H,d), 8.33 (2H,d).

10 **Example 85, Step 3:**

**tert-butyl (1S,2R)-1-{4-[(3-cyanobenzyl)oxy]benzyl}-2-
hydroxy-3-{isobutyl[(4-
nitrophenyl)sulfonyl]amino}propylcarbamate.**

15



[1]: 12 hours; [2]: (1:1); [3]: 95%.

20 ¹H-NMR (DMSO-d₆): δ 0.78 (6H,d+d), 1.19 (9H,s), 1.92
(1H,m), 2.36 (2H,m), 2.80-2.91 (2H,m), 2.98-3.13 (2H,m),
3.32 (1H,m), 3.42 (1H,m), 4.89 (1H,d), 5.07 (2H,s), 6.61
(1H,d), 6.84 (2H,d), 7.04 (2H,d), 7.55 (1H,t), 7.74
(2H,t), 7.83 (1H,s), 8.00 (2H,d), 8.31 (2H,d).

Example 83, Step 5

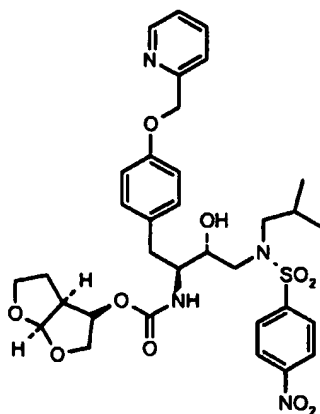
5

General procedure for the addition of BisTHF units

To a solution of the product from the previous step (0.36 g, 0.57 mmol) in 20 mL of anhydrous dichloromethane was
10 added dropwise trifluoroacetic acid (5 mL). The mixture was stirred for 1 hour at room temperature. The solvents were removed under reduced pressure; the residue was redissolved in 50 mL of dichloromethane and 30 mL of 10% aqueous sodium carbonate was added. The aqueous phase
15 was separated and extracted with dichloromethane (2 x 25 mL). The combined organic phases were dried with sodium carbonate, filtered, and concentrated under reduced pressure. The residue was redissolved in 10 mL of acetonitrile. N-Ethyldiisopropylamine (0.15 g, 1.1 mmol)
20 and (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl-4-nitrophenylcarbonate (0.20 g, 0.68 mmol) were added, and the solution was stirred for 12 hours. The solvents were removed under reduced pressure. The residue was redissolved in ethyl acetate (50mL), and the organic
25 phase was extracted with water (30 mL) followed by 5% aqueous sodium carbonate solution (5 x 50 mL). The organic phase was dried with sodium carbonate, filtered, and concentrated under reduced pressure. The residue was purified on silica gel using ethyl acetate-hexanes [1] as
30 eluent to provide the following compounds [Y:(2)]:

-197-

1. (3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-2-hydroxy-3-{isobutyl[(4-nitrophenyl)sulfonyl]amino}-1-[4-(2-pyridinylmethoxy)benzyl]propylcarbamate.



5

[1]: (9:1→100%); [2]: Y: 77%.

¹H-NMR (DMSO-*d*₆): δ 0.77 (3H,d), 0.81 (3H,d), 1.20 (1H,m), 1.32 (1H,m), 1.92 (1H,m), 2.32 (1H,t), 2.72 (1H,m), 2.84-2.89 (2H,dd,b), 2.95-3.00 (1H,m), 3.08-3.14 (1H,m), 3.33 (1H,d), 3.45 (2H,m,b), 3.50-3.57 (2H,m), 3.65 (1H,t), 3.80 (1H,q), 4.80 (1H,q), 4.98 (1H,d), 5.06 (2H,s), 5.46 (1H,d), 6.83 (2H,d), 7.05 (2H,d), 7.18 (1H,d), 7.29 (1H,m), 7.44 (1H,d), 7.78 (1H,m), 8.01 (2H,d), 8.34 (2H,d), 8.52 (1H,d).

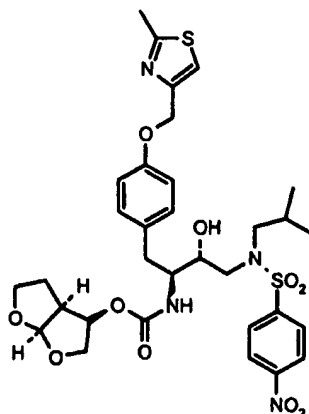
15

Example 84, Step 4:

(3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-2-hydroxy-3-{isobutyl[(4-nitrophenyl)sulfonyl]amino}-1-{4-[(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl}propylcarbamate.

20

-198-



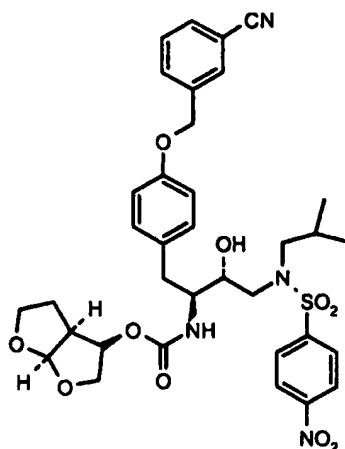
[1]: (8:2); [2]: 59%.

5 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 0.77 (3H,d), 0.81 (3H,d), 1.20
 (1H,m), 1.29-1.36 (1H,m), 1.92 (1H,m), 2.29-2.35 (1H,m),
 2.60 (3H,s), 2.71-2.76 (1H,m), 2.85-2.89 (2H,dd), 2.95-
 3.01 (1H,m), 3.08-3.14 (1H,m), 3.33 (1H,d), 3.45
 (2H,m,b), 3.50-3.58 (2H,m), 3.67 (1H,t), 3.80 (1H,q),
 10 4.80 (1H,q), 4.98 (3H,s,b), 5.47 (1H,d), 6.83 (2H,d),
 7.05 (2H,d), 7.18 (1H,d), 7.47 (1H,s), 8.01 (2H,d), 8.34
 (2H,d).

Example 85, Step 4:

(3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-{4-
 15 [(3-cyanobenzyl)oxy]benzyl}-2-hydroxy-3-{isobutyl[(4-
 nitrophenyl)sulfonyl]amino}propylcarbamate.

-199-



[1]: (2:8); [2]: 74%.

5

¹H-NMR (DMSO-d₆): δ 0.76 (3H,d), 0.80 (3H,d), 1.16-1.20
 10 (1H,m), 1.27-1.37 (1H,m), 1.92 (1H,m), 2.32 (1H,t), 2.72
 (1H,m), 2.86 (2H,dd), 2.94-3.00 (1H,m), 3.08-3.14 (1H,m),
 3.33 (1H,d), 3.45 (2H,m,b), 3.50-3.58 (2H,m), 3.65
 (1H,t), 3.80 (1H,q), 4.80 (1H,q), 4.98 (1H,d), 5.06
 (2H,s), 5.46 (1H,d), 6.83 (2H,d), 7.06 (2H,d), 7.18
 15 (1H,d), 7.56 (1H,t), 7.74 (2H,t), 7.84 (1H,s), 8.00
 (2H,d), 8.33 (2H,d).

Example 83, Step 6

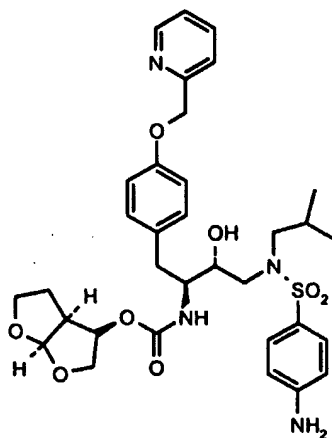
20 General procedure for the reduction of the nitro group

To a stirred solution of the product obtained from the previous step (0.23 g, 0.34 mmol) in 4 mL of anhydrous tetrahydrofuran was added 70 mg of platinum (on activated

-200-

carbon, 3% Pt). The mixture was stirred under an atmospheric pressure of hydrogen for the indicated number of hours [1]. The catalyst was filtered, and the solvent was removed under reduced pressure. The residue was
 5 purified on silica gel using ethyl acetate-hexanes [2] as eluent to provide the following compounds (Y:[3]):

(3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 10 [[(4-aminophenyl)sulfonyl]-(isobutyl)amino]-2-hydroxy-1-
 [4-(2-pyridinylmethoxy)benzyl]propylcarbamate (299)



15

[1]: 12 hours; [2]: (9:1); [3]: 90%*.

¹H-NMR (DMSO-*d*₆): δ 0.74 (3H,d), 0.81 (3H,d), 1.20-1.16
 (1H,m), 1.29 (1H,m), 1.89 (1H,m), 2.34 (1H,t), 2.54-2.66
 20 (2H,m), 2.71 (1H,m), 2.86-2.96 (2H,m), 3.22,3.25 (1H,dd),
 3.40-3.59 (4H,m,b), 3.65 (1H,t), 3.82 (1H,m), 4.80
 (1H,q), 4.92,4.95 (1H,dd), 5.06,5.08 (2H,s), 5.46 (1H,d),
 5.94 (1H,s), 6.54 (1H,d), 6.82 (3H,m), 7.08 (2H,d), 7.20
 (1H,m), 7.31 (2H,m), 7.44 (1H,d), 7.49 (1H,d), 7.78

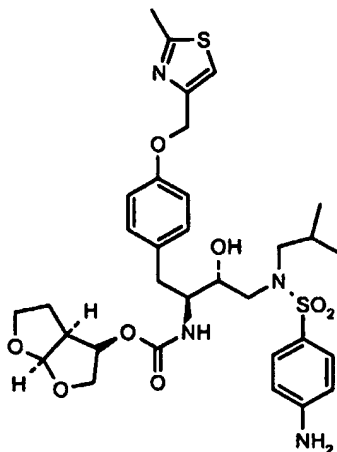
-201-

(1H,t), 8.52 (2H,d), 8.64 (s)*, 8.94 (s)*. MS: 657 (M⁺), 673 (M⁺)*.

*Note: This was obtained as a 3:1 mixture with respect
5 to the hydroxylamine derivative (by ¹H NMR).

Example 84 Step 5:

(3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
10 [[(4-aminophenyl)sulfonyl]-(isobutyl)amino]-2-hydroxy-1-
{4-[(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl}
propylcarbamate (300)



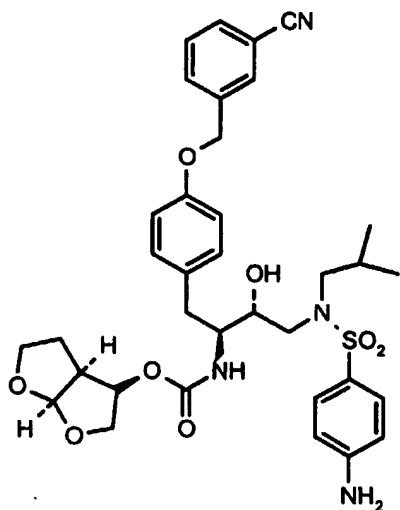
15

[1]: 77 hours; [2]: (9:1); [3]: 53%.

¹H-NMR (DMSO-*d*₆): δ 0.75 (3H,d), 0.81 (3H,d), 1.19
(1H,m), 1.32 (1H,m), 1.89 (1H,m), 2.35 (1H,t), 2.54-2.69
20 (5H, dd+s), 2.72 (1H,m), 2.87-2.93 (2H,m), 3.22 (1H,d),
3.47 (1H,m), 3.53-3.60 (3H,m), 3.68 (1H,t), 3.82 (1H,dd)
4.80 (1H,q), 4.93 (1H,m), 4.98 (2H,s,b), 5.47 (1H,d),
5.94 (2H,s,b), 6.55 (2H,d), 6.83 (2H,d), 7.07 (2H,d),
7.19 (1H,d), 7.33 (2H,d), 7.47 (1H,s). MS: 676 (M⁺).

Example 85, Step 5:

- 5 **(3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [[(4-aminophenyl)sulfonyl]-(isobutyl)amino]-1-{4-[(3-
 cyanobenzyl)oxy]benzyl}-2-hydroxypropylcarbamate (301)**



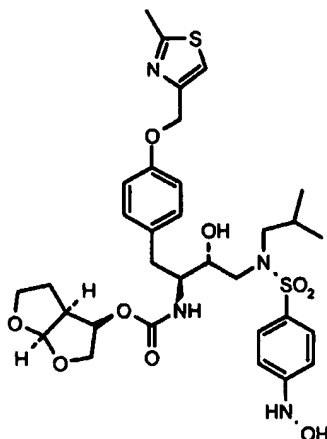
analytical data see Example 301 (Route 1) above

10

Example 86

- (3*S*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-2-
 hydroxy-3-[[4-(hydroxyamino)benzyl](isobutyl)amino]-1-{4-
 15 [(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl}
 propylcarbamate (302)**

-203-



[1]: 3 hours; [2]: no purification; [3]: quantitative.

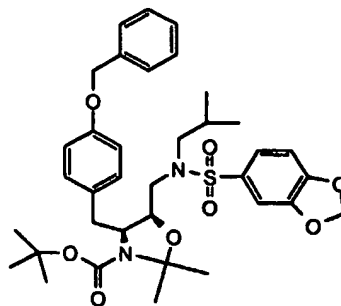
5 $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 0.74 (3H,d), 0.81 (3H,d), 1.15-1.20 (1H,m), 1.34 (1H,m), 1.90 (1H,m), 2.35 (1H,t), 2.60-2.75 (7H, m+s), 2.87-2.96 (1H,m), 3.29 (1H,d,b), 3.42-3.56 (4H,m), 3.68 (1H,t), 3.82 (1H,dd), 4.80 (1H,q), 4.98,4.95 (3H,s+d), 5.47 (1H,d), 6.82,6.84 (4H,d+d), 7.07 (2H,d),
 10 7.20 (1H,d), 7.48,7.51 (3H,sd), 8.64 (1H,s), 8.94 (1H,s).
 MS: 676 (M^+).

Example 87

Step 1:

15 t-butyl (4S,5R)-5-{[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-4-[4-(benzyloxy)benzyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate

-204-



The reaction was carried out as described for analogous transformations above, starting with previously described
 5 tert-butyl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-(benzyloxy)benzyl]-2-hydroxypropylcarbamate

The residue was purified on silica gel hexane-ethyl acetate (3:1) as eluant to afford 2.68g (88%) of the
 10 title compound.

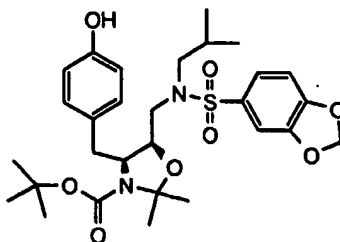
¹H-NMR: (CDCl₃): δ 0.86 (3H,d), 0.98 (3H,d), 1.40, 1.45 (3H,s)*, 1.50, 1.55 (3H,s)*, 1.64 (3H,s), 1.66 (3H,s), 1.68 (3H,s), 1.99 (1H,m), 2.65-3.09 (5H,m), 3.24-3.32
 15 (1H,m), 4.17-4.28 (2H,m), 5.09 (2H,s), 6.05 (2H,s), 6.82 (1H,d), 6.96 (2H,d), 7.05-7.18 (4H,m), 7.29-7.50 (5H,m).
 MS: 667 (M⁺). C₃₆H₄₆N₂O₈S.

*: Possible indication for rotamers.

20

Step 2:

t-butyl (4*S*,5*R*)-5-{[1,3-benzodioxol-5-ylsulfonyl](isobutyl)amino]methyl}-4-(4-hydroxybenzyl)-
 25 2,2-dimethyl-1,3-oxazolidine-3-carboxylate.



The reaction was carried out as described previously
 5 starting from t-butyl (4S,5R)-5-{[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-4-[4-(benzyloxy)benzyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate to afford 2.31 g (100%) of the title compound.

10

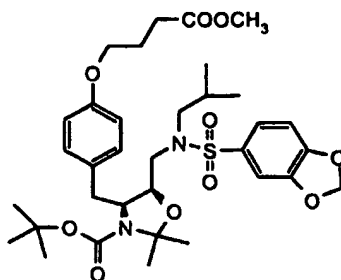
$^1\text{H-NMR}$: (CDCl_3): δ 0.86 (3H,d), 0.98 (3H,d), 1.40, 1.45 (3H,s)*, 1.50, 1.55 (3H,s)*, 1.66 (3H,s), 1.68 (3H,s), 1.70 (3H,s), 1.99 (1H,m), 2.63-3.09 (5H,m), 3.23-3.31 (1H,m), 3.80 (1H,m), 4.14-4.27 (2H,m), 6.11 (2H,s), 6.77-
 15 6.87 (3H,m), 7.02-7.19 (4H,m). MS: 576 (M^+). $\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_8\text{S}$.

*: Possible indication for rotamers.

20 Step 3:

t-butyl (4S,5R)-5-{[1,3-benzodioxol-5-ylsulfonyl](isobutyl)amino]methyl}-4-{4-(4-methoxy-4-oxobutoxy)benzyl}-2,2-dimethyl-1,3-oxazolidine-3-
 25 carboxylate

-206-



The reaction was carried out as described previously for
 5 analogous transformations, starting from 1.83 g (3.17
 mmol) of t-butyl (4S,5R)-5-{[1,3-benzodioxol-5-
 ylsulfonyl] (isobutyl) amino]methyl}-4-(4-hydroxybenzyl)-
 2,2-dimethyl-1,3-oxazolidine-3-carboxylate except methyl-
 4-iodobutyrate was used as alkylating reagent.

10

[2]: room temperature; [3]: 5 hours.

The residue was purified on silica gel using hexane-ethyl
 acetate (2:1/1:1) as eluant to afford 2.1g (98%) of the
 15 title compound.

¹H-NMR: (CDCl₃): δ 0.86 (3H,d), 0.98 (3H,d), 1.36, 1.38
 (3H,s)*, 1.44, 1.49 (3H,s)*, 1.56 (3H,s), 1.59 (3H,s),
 1.64 (3H,s), 1.99 (1H,m) 2.14-2.19 (1H,m), 2.47-3.08
 20 (7H,m), 3.23-3.30 (2H,m), 3.72 (3H,s), 4.03-4.27 (4H,m),
 6.10 (2H,s), 6.80-6.87 (3H,m), 7.06-7.19 (4H,m). MS: 677
 (M⁺). C₃₄H₄₈N₂O₁₀S.

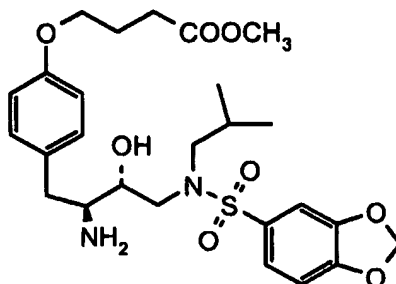
*: Possible indication for rotamers.

25

Step 4:

-207-

Methyl 4-(4-{(2S,3R)-2-amino-4-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-3-hydroxybutyl}phenoxy)butanoate



5

The reaction was carried out as described previously for similar transformations starting t-butyl (4S,5R)-5-[[1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-4-{4-(methoxy-4-oxobutoxy)benzyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate, to afford 1.6g (96%) of the title compound.

Used in the next step without further purification.

¹H-NMR: (Methanol-d₄): δ 0.86 (3H,d), 0.98 (3H,d), 1.99 (1H,m), 2.02-2.92 (3H,m), 2.45-2.60 (2H,m), 2.67-3.17 (6H,m), 3.28-3.47 (2H,m), 3.57-3.62 (1H,m), 3.70 (3H,s), 3.75-3.82 (1H,m), 3.92-4.18 (2H,m), 6.14 (2H,s), 6.81-7.03 (4H,m), 7.13-7.22 (2H,m), 7.39 (1H,d). MS: 537 (M⁺).
C₂₆H₃₆N₂O₈S.

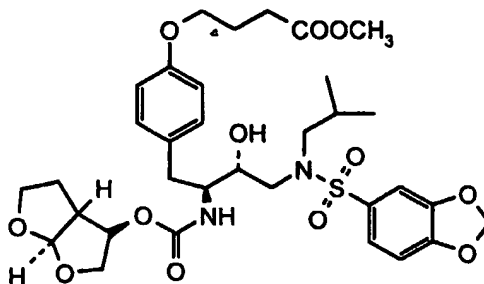
20

Step 5:

Methyl 4-(4-{(2S,3R)-2-([3R,3aS,6aR]-hexahydrofuro[2,3-b]furan-3-yloxy)carbonyl}amino)-4-[(1,3-benzodioxol-5-

25

ylsulfonyl) (isobutyl) amino] -3-hydroxybutyl}phenoxy)
butanoate (303)



5

The reaction was carried out as described previously for
analogous transformations, starting Methyl 4-(4-{(2S,3R)-
2-amino-4-[(1,3-benzodioxol-5-
ylsulfonyl) (isobutyl) amino] -3-
hydroxybutyl}phenoxy)butanoate

The residue was purified by silica gel using hexane-ethyl
acetate (2:1/1:1/1:2) as eluant to afford 0.91 g (44%) of
the title compound.

15

¹H-NMR: (CDCl₃): δ 0.94 (3H,d), 1.00 (3H,d), 1.25-1.35
(1H,m), 1.56-1.69 (2H,m), 1.89 (1H,m), 2.08-2.18 (3H,m),
2.53-2.58 (2H,m), 2.75-2.82 (2H,m), 2.84-3.13 (4H,m),
3.18-3.21 (2H,m), 3.61 (1H,s), 3.72 (3H,s), 3.78-3.97
(2H,m), 4.01-4.17 (3H,m), 4.90 (1H,d), 5.06 (1H,q), 5.70
(1H,d), 6.13 (2H,s), 6.83 (2H,d), 6.93 (1H,d), 7.13-7.19
(3H,m), 7.37 (1H,d). MS: 693 (M⁺). C₃₃H₄₄N₂O₁₂S.

25

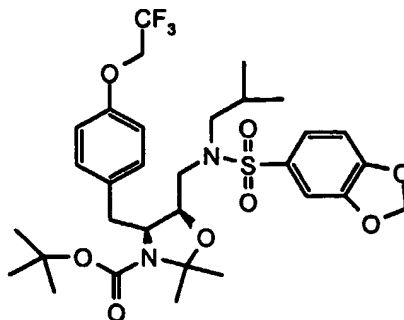
Example 88

Step 1:

-209-

t-butyl (4S,5R)-5-{[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-2,2-dimethyl-4-[4-(2,2,2-trifluoroethoxy)benzyl]-1,3-oxazolidine-3-carboxylate

5



To a solution of t-butyl (4S,5R)-5-{[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-4-(4-hydroxybenzyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (0.25 g, 0.433 mmol) in 6 ml of dichloromethane-THF (2:1) was added tetrabutylammonium hydrogensulfate (8.9 mg, 0.026 mmol), 40% aqueous sodium hydroxide (0.136 ml) and 2,2,2-trifluoroethyltrifluoromethanesulfonate (100 mg, 0.433 mmol). The mixture was heated to reflux for 2.5 hours. Diluted with 10 ml of dichloromethane and 10 ml of water and the organic phase was separated, dried with sodium sulfate, filtered and concentrated under reduced pressure.

The residue was purified on silica gel using hexane-ethyl acetate (2:1) as eluant to afford 90 mg (32%) of the title compound.

¹H-NMR: (CDCl₃): δ 0.87 (3H,d), 0.96 (3H,d), 1.45, 1.48 (3H,s)*, 1.51, 1.57 (3H,s)*, 1.60 (3H,s), 1.62 (3H,s), 1.65

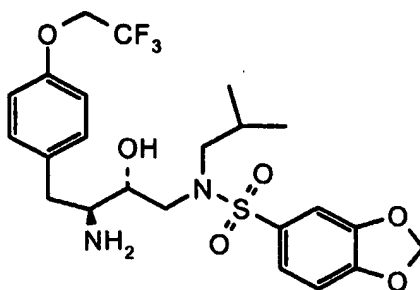
-210-

(3H,s), 1.99 (1H,m), 2.68-3.19 (5H,m), 3.25-3.30 (1H,m),
 4.26-4.40 ((4H,m), 6.09 (2H,s), 6.81-7.01 (4H,m), 7.17-
 7.29 (3H,m). MS: 659 (M⁺). C₃₁H₄₁F₃N₂O₈S.

5 *: Possible indication for rotamers.

Step 2:

N-{(2R,3S)-3-amino-2-hydroxy-4-[4-(2,2,2-
 10 trifluoroethoxy)phenyl]butyl}-N-isobutyl-1,3-
 benzodioxole-5-sulfonamide



15

The reaction was carried out as previously for similar
 transformations from t-butyl (4S,5R)-5-{[(1,3-
 benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-2,2-
 dimethyl-4-[4-(2,2,2-trifluoroethoxy)benzyl]-1,3-
 20 oxazolidine-3-carboxylate to afford 70 mg (99%) of the
 title compound.

Used in the next step without further purification.

¹H-NMR: (DMSO-d₆): δ 0.78 (3H,d), 0.84 (3H,d), 1.99
 25 (1H,m), 2.60-3.58 (11H,m), 4.72-4.84 (2H,m), 6.16 (2H,s),

-211-

6.93-7.18 (4H,m), 7.21-7.34 (3H,m). MS: 519 (M⁺).

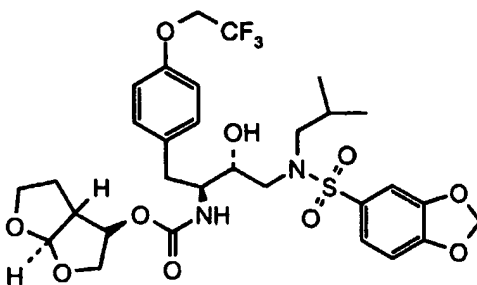
C₂₃H₂₉F₃N₂O₆S.

Step 3:

5

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
hydroxy-1-[4-(2,2,2-trifluoroethoxy)benzyl]
propylcarbamate (304)

10



15 The reaction was carried out as described previously for
similar transformations from N-[(2R,3S)-3-amino-2-
hydroxy-4-[4-(2,2,2-trifluoroethoxy)phenyl]butyl]-N-
isobutyl-1,3-benzodioxole-5-sulfonamide

The residue was purified by silica gel using hexane-ethyl
20 acetate (1:1) as eluant to afford 43 mg (47%) of the
title compound.

¹H-NMR: (CDCl₃): δ 0.86 (3H,d), 0.95 (3H,d), 1.31-1.39
(1H,m), 1.59-1.88(4H,m), 2.79-2.86 (2H,m), 2.97-3.08
25 (2H,m), 3.12-3.20 (2H,m), 3.64-4.06 (6H,m), 4.32-4.40
(2H,m), 4.75 (1H,d), 5.05 (1H,q), 5.70 (1H,d), 6.13

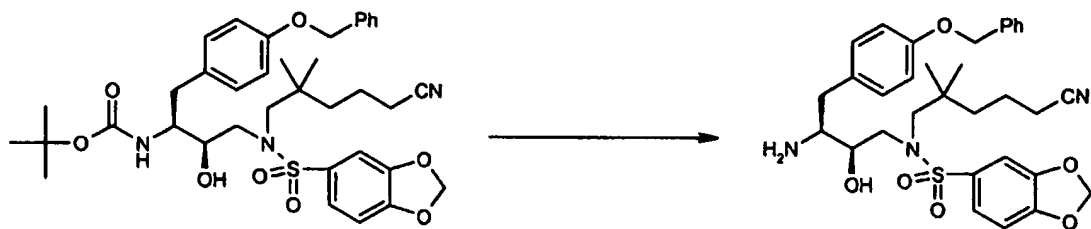
-212-

(2H, s), 6.89-6.99 (3H, m), 7.15-7.29 (3H, m), 7.36 (1H, d).

MS: 675 (M⁺). C₃₀H₃₇F₃N₂O₁₀S.**Example 89**

5 Step1:

***N*-{(2*R*,3*S*)-3-Amino-4-[4-(benzyloxy)phenyl]-2-hydroxybutyl}-*N*-(5-cyano-2,2-dimethylpentyl)-1,3-benzodioxole-5-sulfonamide**



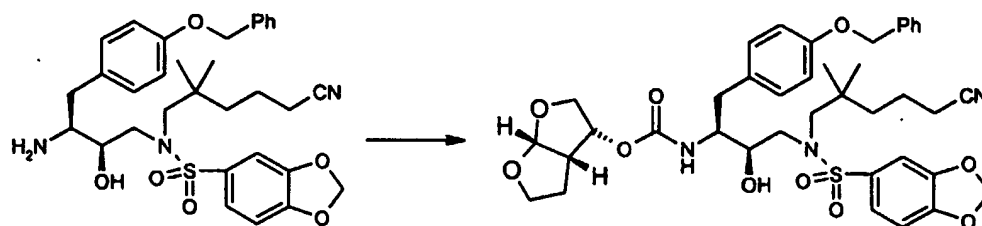
10

Treatment of tert-butyl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(5-cyano-2,2-dimethylpentyl)amino]-1-[4-(benzyloxy)benzyl]-2-hydroxypropylcarbamate with
 15 trifluoroacetic acid/dichloromethane as previously described provided the title compound as a solid foam. ¹H
 NMR (DMSO-*d*₆): δ 0.95 (6H, s), 1.15 (1H, br d), 1.2-1.6
 (5H, m), 2.2 (1H, t), 2.42 (2H, br s), 2.6 (2H, br d),
 2.9 (1H, d), 3.05 (1H, dd), 3.3 (1H, br s), 3.45 (2H, br
 20 d), 4.62 (1H, s), 5.0 (2H, s), 6.15 (2H, s), 6.89 (2H,
 d), 7.0 (1H, d), 7.06 (2H, d), 7.22-7.42 (7H, m); MS: 594
 (MH⁺)

Step 2:

25 **(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(5-cyano-2,2-**

dimethylpentyl) amino] -1- [4- (benzyloxy) benzyl] -2-
hydroxypropylcarbamate (305)



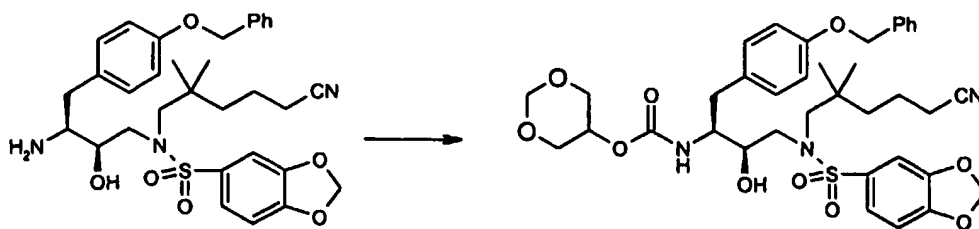
5 *N*-{ (2*R*, 3*S*) -3-Amino-4- [4- (benzyloxy) phenyl] -2-
hydroxybutyl} -*N*- (5-cyano-2,2-dimethylpentyl) -1,3-
benzodioxole-5-sulfonamide was treated with
[(3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*] furan-3-yl] [4-
nitrophenyl] carbonate, diisopropylethylamine and
10 acetonitrile as previously described to provide the title
compound as a solid foam. ¹H NMR (DMSO-*d*₆): δ 0.87 (3H,
s), 0.92 (3H, s), 1.10-1.13 (1H, m), 1.32-1.38 (3H, m),
1.5-1.6 (2H, m), 2.33 (1H, t), 2.4 (2H, t), 2.65-2.75
(2H, m), 2.7-2.9 (2H, m), 3.3-3.4 (3H, m), 3.5-3.6 (2H,
15 m), 3.65 (1H, t), 3.7 (1H, dd), 3.8 (1H, dd), 4.8 (1H,
dd), 5.0 (2H, s), 5.03 (1H, d), 5.45 (1H, d), 6.15 (2H,
s), 6.82 (2H, d), 7.03 (1H d), 7.04 (2H, d), 7.16 (1H,
d), 7.22 (1H, s), 7.26-7.40 (6H, m); MS: 750 (MH⁺);

20

Example 90

1,3-Dioxan-5-yl (1*S*, 2*R*) -3- [(1,3-benzodioxol-5-
ylsulfonyl) (5-cyano-2,2-dimethylpentyl) amino] -1- [4-
(benzyloxy) benzyl] -2-hydroxypropylcarbamate (306)

-214-

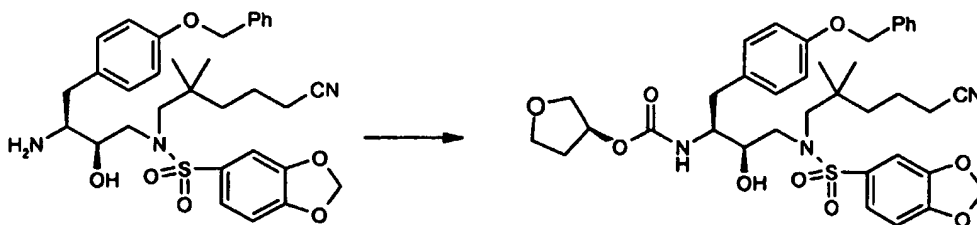


N-((2R,3S)-3-Amino-4-[4-(benzyloxy)phenyl]-2-hydroxybutyl)-N-(5-cyano-2,2-dimethylpentyl)-1,3-benzodioxole-5-sulfonamide was treated with 1,3-dioxan-5-yl 4-nitrophenyl carbamate/diisopropylamine/acetonitrile as previously described to afford the title compound as a solid foam. ¹H NMR (DMSO-d₆): δ 0.88 (3H, s), 0.89 (3H, s), 1.3-1.4 (2H, m), 1.5-1.6 (2H, m), 2.4-2.5 (3H, m), 2.70-2.82 (2H, m), 2.95 (1H, dd), 3.3-3.4 (3H, m), 3.5 (1H, d), 3.65-3.75 (2H, m), 3.79 (1H, d), 3.89 (1H, d), 4.25 (1H, s), 4.65 (1H, d), 4.8 (1H, d), 4.97 (1H, d), 5.0 (2H, s), 6.15 (2H, s), 6.84 (2H, d), 7.0 (1H, d), 7.15 (2H, d), 7.2 (1H, d), 7.25 (1H, s), 7.26-7.40 (6H, m); MS: 724 (MH⁺)

15

Example 91

(3S)-Tetrahydro-3-furanyl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(5-cyano-2,2-dimethylpentyl)amino]-1-[4-(benzyloxy)benzyl]-2-hydroxypropylcarbamate (307)



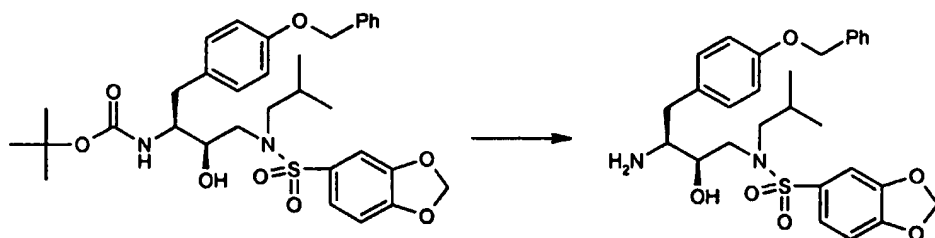
N-{(2*R*,3*S*)-3-Amino-4-[4-(benzyloxy)phenyl]-2-hydroxybutyl}-*N*-(5-cyano-2,2-dimethylpentyl)-1,3-benzodioxole-5-sulfonamide was treated with 1-([[(3*S*)-tetrahydro-3-furanyloxy]carbonyl]oxy)-2,5-pyrrolidinedione/diisopropylamine/acetonitrile as previously described to provide the title product as a solid foam. ¹H NMR (DMSO-*d*₆): δ 0.88 (3H, s), 0.90 (3H, s), 1.3 (2H, dd), 1.5-1.6 (2H, m), 1.7-1.8 (1H, m), 2.0-2.2 (1H, m), 2.37 (1H, t), 2.4 (2H, t), 2.75-2.85 (3H, m), 2.9 (1H, dd), 3.30-3.45 (3H, m), 3.55 (1H, dd), 3.65 (1H, dd), 3.7 (2H, dd), 4.9 (1H, s), 4.98 (1H, d), 5.0 (2H, s), 6.15 (2H, s), 6.8 (2H, d), 7.0 (2H, d), 7.06 (2H, d), 7.24 (1H, s), 7.25-7.42 (6H, m); MS: 708 (MH⁺);

15

Example 92

Step 1:

N-{(2*R*,3*S*)-3-Amino-4-[4-(benzyloxy)phenyl]-2-hydroxybutyl}-*N*-isobutyl-1,3-benzodioxole-5-sulfonamide (308)



Treatment of *tert*-butyl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-yl)(isobutyl)amino]-1-[4-(benzyloxy)benzyl]-2-hydroxypropylcarbamate with trifluoroacetic acid as previously described afforded the title compound as a solid foam. ¹H NMR (DMSO-*d*₆): δ 0.90 (3H, d), 0.94 (3H,

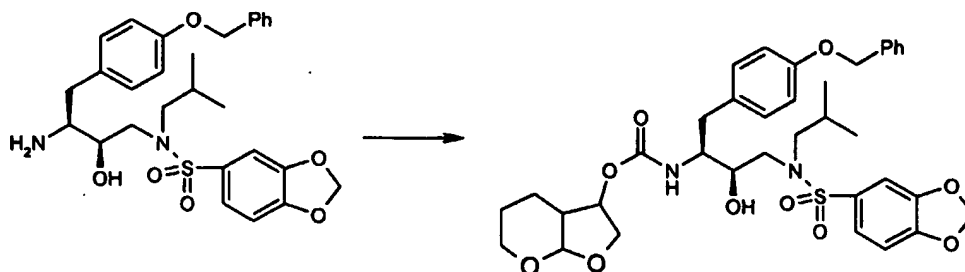
25

-216-

d), 1.8-2.0 (2H, m), 2.3 (1H, dd), 2.70-2.85 (3H, m),
 2.9-3.0 (2H, m), 3.2-3.3 (2H, m), 3.4-3.5 (2H, m), 4.7
 (1H, d), 5.03 (2H, s), 6.18 (2H, s), 6.9 (2H, d), 7.02
 (1H, d), 7.1 (2H, d), 7.24 (1H, s), 7.25-7.43 (5H, m);
 5 MS: 527 (MH⁺)

Step 2:

Hexahydro-4H-furo[2,3-b]pyran-3-yl (1S,2R)-3-[(1,3-
 benzodioxol-5-ylsulfonyl) (isobutyl) amino]-1-[4-
 10 (benzyloxy)benzyl]-2-hydroxypropylcarbamate



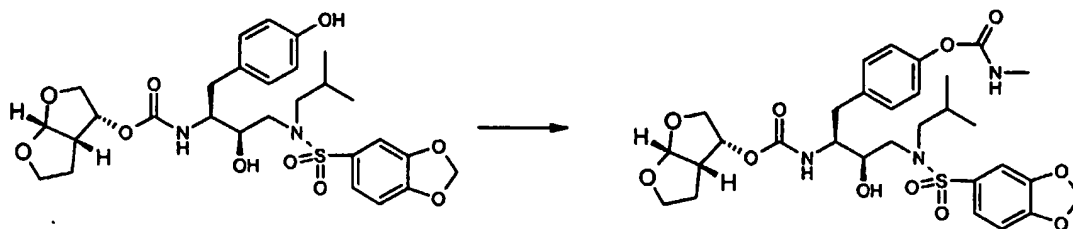
N-{(2*R*,3*S*)-3-Amino-4-[4-(benzyloxy)phenyl]-2-
 hydroxybutyl}-*N*-isobutyl-1,3-benzodioxole-5-sulfonamide
 15 was treated with hexahydro-4*H*-furo[2,3-*b*]pyran-3-yl 4-
 nitrophenyl carbonate/diisopropylethylamine/acetonitrile
 as previously described to afford after silica gel
 chromatography (dichloromethane/methanol, 49:1) the title
 diastereomers as a solid foams. Diastereomer A: ¹H NMR
 20 (DMSO-*d*₆): δ 0.76 (3H, d), 0.80 (3H, d), 1.2 (1H, br s),
 1.6 (2H, br s), 1.9 (1H, br s), 2.1 (1H, br s), 2.4 (1H,
 br s), 2.75 (1H, dd), 2.8-3.0 (3H, m), 3.2-3.3 (3H, m),
 3.4-3.6 (3H, m), 3.7 (1H, d), 4.0 (1H, t), 4.8-4.9 (2H,
 m), 5.0 (3H, br s), 6.15 (2H, s), 6.8 (2H, d), 7.0-7.2
 25 (4H, m), 7.21-7.42 (7H, m); MS: 719 (M+23) Diastereomer
 B: ¹H NMR (DMSO-*d*₆): δ 0.76 (3H, d), 0.82 (3H, d), 1.0
 (1H, br s), 1.3 (1H, br s), 1.5 (1H, br s), 1.95 (2H, br

-217-

s), 2.4 (1H, t), 2.7 (2H, td), 2.9 (1H, d), 2.97 (1H, dd), 3.2-3.3 (3H, m), 3.5 (1H, br s), 3.55 (1H, br s), 3.64 (2H, br s), 4.0 (1H, dd), 4.9 (1H, s), 4.95-5.05 (4H, m), 6.15 (2H, s), 6.8 (2H, d), 7.0-7.2 (4H, m), 7.22 (1H, s), 7.25-7.40 (6H, m); MS: 719 (M+23)

Example 93

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 10 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-{[(methylamino)carbonyl]oxy}benzyl)propylcarbamate (309)



15

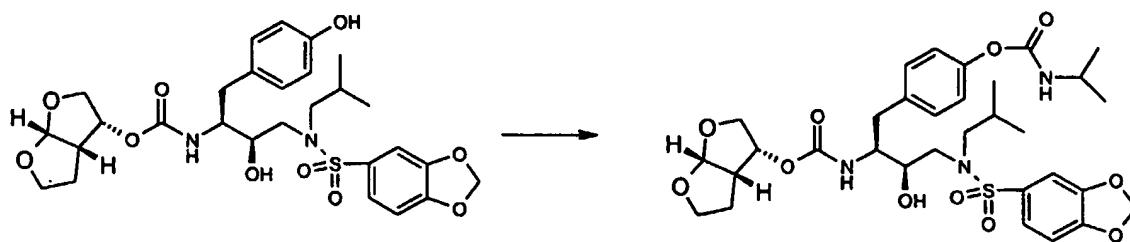
A mixture of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-hydroxybenzyl)propylcarbamate (80 mg), methyl isocyanate
 20 (0.5 mL), dichloromethane (3 mL) and diisopropylamine (0.05 mL) was stirred at ambient temperature for 1 h. Solvent was evaporated and the residue was purified by chromatography (silica gel, hexanes/ethyl acetate, 3:1) to provide the title compound as a solid foam (57 mg). ¹H
 25 NMR (DMSO-d₆): δ 0.78 (3H, d), 0.82 (3H, d), 1.17 (1H, dd), 1.30-1.45 (1H, m), 1.9-2.0 (1H, m), 2.42 (1H, t), 2.6 (3H, d), 2.62-2.80 (3H, m), 2.99 (2H, dd), 3.15-3.20

-218-

(1H, m), 3.50-3.63 (4H, m), 3.7 (1H, t), 3.8 (1H, dd),
 4.8 (1H, dd), 5.04 (1H, d), 5.5 (1H, d), 6.18 (2H, s),
 6.95 (2H, d), 7.05 (1H, d), 7.15 (2H, d), 7.2 (1H, s),
 7.25 (1H, d), 7.5 (1H, quartet), 8.08 (1H, d); MS: 650
 5 (MH⁺).

Example 94

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 10 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-(4-{[(isopropylamino)carbonyl]oxy}
 benzyl)propylcarbamate (310)

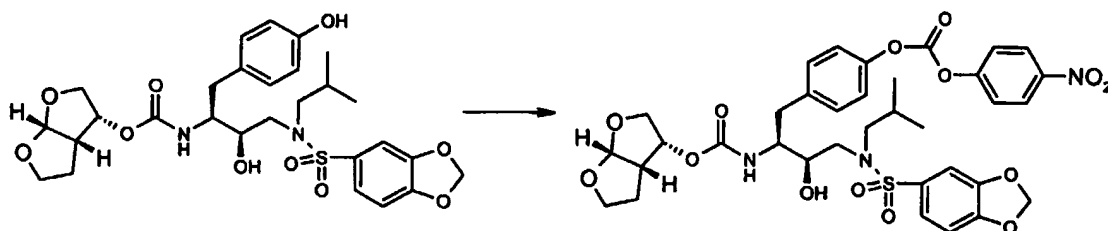


15 (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-(4-hydroxybenzyl)propylcarbamate was treated
 with isopropyl isocyanate/triethylamine/dichloromethane
 as described in Example 93 to provide the title compound
 20 as a solid foam. ¹H NMR (DMSO-d₆): δ 0.76 (3H, d), 0.82
 (3H, d), 0.98 (3H, d), 1.1 (3H, d), 1.35-1.42 (1H, m),
 1.90-1.95 (1H, m), 2.4 (1H, t), 2.65-2.80 (3H, m), 2.9-
 3.0 (2H, m), 3.3-3.4 (1H, m), 3.50-3.63 (6H, m), 3.7 (1H,
 t), 3.8 (1H, dd), 4.8 (1H, dt), 5.05 (1H, br d), 5.45
 25 (1H, d), 6.18 (2H, s), 6.92 (2H, d), 7.0 (1H, d), 7.18
 (2H, d), 7.22 (1H, s), 7.3 (2H, d), 7.58 (1H, d); MS: 678
 (MH⁺); C₃₂H₄₃N₃O₁₁S.

Example 95

Step 1:

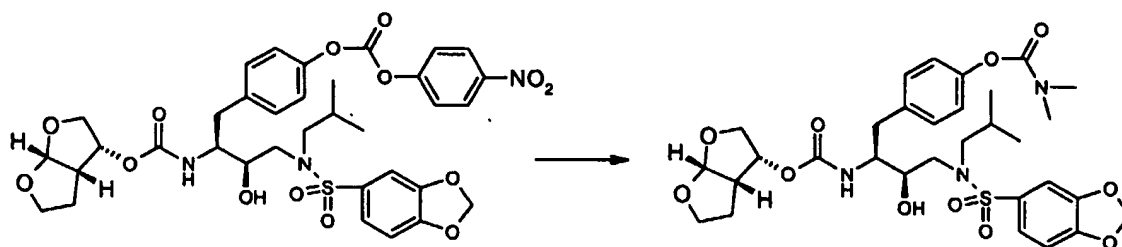
4-{(2*S*,3*R*)-2-({[(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-
 yloxy]carbonyl}amino)-4-[(1,3-benzodioxol-5-
 5 ylsulfonyl)(isobutyl)amino]-3-hydroxybutyl}phenyl 4-
 nitrophenyl carbonate



To a solution of (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-
 10 3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-
 ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-
 hydroxybenzyl)propylcarbamate (0.5 g, 0.84 mmol) in
 dichloromethane (4 mL) at 0°C was added pyridine (0.16 mL,
 0.158 g, 2.0 mmol) and 4-nitrophenyl chloroformate (0.22
 15 g, 1.09 mmol) and the mixture was stirred at ambient
 temperature for 1 h. Dichloromethane was added and the
 mixture was washed with 15% citric acid/water (2X),
 saturated sodium bicarbonate/water, dried (sodium
 sulfate), evaporated, and purified by chromatography
 20 (silica gel, dichloromethane/methanol, 49:1) to provide
 the title compound as a solid foam (0.5 g, 79% yield). ¹H
 NMR (DMSO-*d*₆): δ 0.78 (3H, d), 0.82 (3H, d), 1.16 (1H,
 dd), 1.3-1.4 (1H, m), 1.9-2.0 (1H, m), 2.42 (1H, t),
 2.65-2.80 (3H, m), 3.0 (2H, dd), 3.3-3.4 (1H, m), 3.5-3.6
 25 (4H, m), 3.7 (1H, t), 3.8 (1H, dd), 4.8 (1H, dt), 5.1
 (1H, d), 5.5 (1H, d), 6.18 (2H, s), 7.05 (1H, d), 7.2-7.4
 (7H, m), 7.7 (2H, d), 8.35 (2H, d)

Step 2:

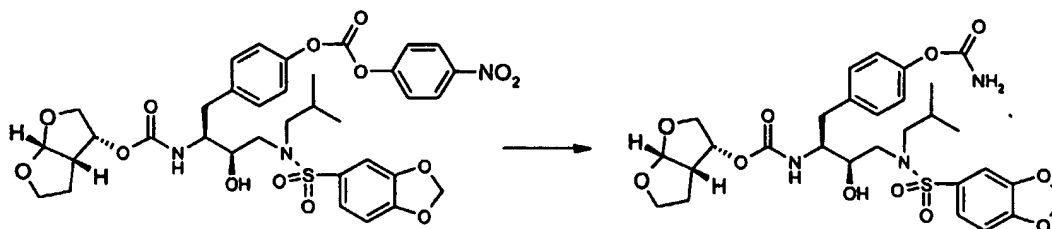
(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-(4-
 5 {[(dimethylamino)carbonyl]oxy}benzyl)-2-
 hydroxypropylcarbamate (311)



To a solution of 4-[(2S,3R)-2-[(3R,3aS,6aR)-
 10 Hexahydrofuro[2,3-b]furan-3-yloxy]carbonyl]amino)-4-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-3-
 hydroxybutyl}phenyl 4-nitrophenyl carbonate (60 mg) in
 tetrahydrofuran (0.5 mL) was added 2M
 dimethylamine/tetrahydrofuran (0.5 mL) and the mixture
 15 was stirred at ambient temperature for 30 min. Ethyl
 acetate was added and the mixture was washed with
 saturated sodium bicarbonate/water (4X), dried (sodium
 sulfate), evaporated, and purified by chromatography
 (silica gel, hexanes/ethyl acetate, 3:7) to provide the
 20 title compound as a solid foam. ¹H NMR (DMSO-d₆): δ 0.76
 (3H, d), 0.82 (3H, d), 1.1-1.2 (1H, m), 1.2 (1H, br
 quintuplet), 1.9-2.0 (1H, m), 2.2 (1H, t), 2.6-2.8 (3H,
 m), 2.81 (3H, s), 2.9 (3H, s), 3.0 (1H, br s), 3.2-3.3
 (2H, m), 3.4-3.6 (4H, m), 3.7 (1H, t), 3.8 (1H, dd), 4.8
 25 (1H, dt), 5.0 (1H, br s), 5.5 (1H, d), 6.1 (2H, s), 6.9
 (2H, d), 7.0 (1H, d), 7.15 (2H, d), 7.19 (1H, s), 7.22
 (2H, br d); MS: 664 (MH⁺); C₃₁H₄₁N₃O₁₁S.

Example 96A

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-{4-
 [(aminocarbonyl)oxy]benzyl}-3-[(1,3-benzodioxol-5-
 ylsulfonyl)(isobutyl)amino]-2-hydroxypropylcarbamate
 5 (312)



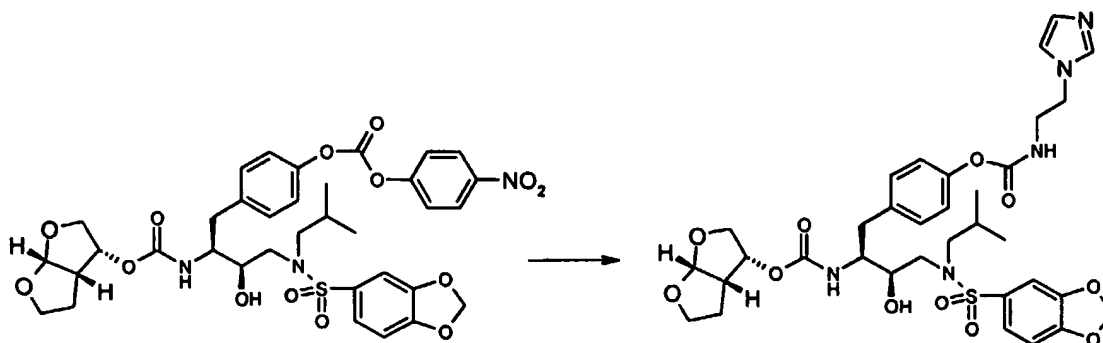
4-[(2S,3R)-2-({[(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-
 yloxy]carbonyl}amino)-4-[(1,3-benzodioxol-5-
 10 ylsulfonyl)(isobutyl)amino]-3-hydroxybutyl]phenyl 4-
 nitrophenyl carbonate was treated with concentrated
 ammonium hydroxide as described in Example 311 to afford
 the title compound as a white solid. ¹H NMR (DMSO-d₆): δ
 0.78 (3H, d), 0.86 (3H, d), 1.2 (1H, dd), 1.4 (1H, br
 15 quintuplet), 1.85-1.95 (1H, m), 2.2 (1H, t), 2.65-2.80
 (3H, m), 2.9-3.0 (2H, m), 3.25-3.30 (1H, m), 3.5-3.6 (4H,
 m), 3.7 (1H, t), 3.8 (1H, dd), 4.8 (1H, dt), 5.0 (1H, d),
 5.4 (1H, d), 6.18 (2H, d), 6.8 (2H, br d), 6.9 (2H, d),
 7.0 (1H, d), 7.15 (2H, d), 7.2 (1H, s), 7.25-7.30 (2H,
 20 m); MS: 636 (MH⁺).

Example 96B

25 (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-

-222-

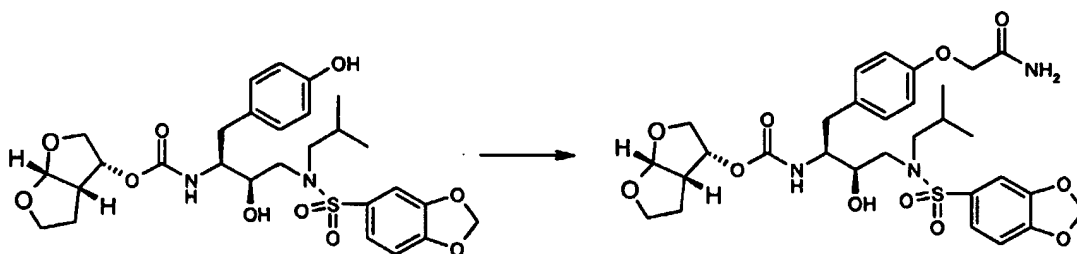
hydroxy-1-{4-[(2-(1H-imidazol-1-yl)ethyl)amino]
carbonyl)oxy]benzyl}propylcarbamate (313)



- 5 To a solution of 4-{(2*S*,3*R*)-2-([(3*R*,3*aS*,6*aR*)-
Hexahydrofuro[2,3-*b*]furan-3-yloxy]carbonyl)amino)-4-
[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-3-
hydroxybutyl}phenyl 4-nitrophenyl carbonate (50 mg, 0.07
mmol) in 1,4-dioxane (1 mL) was added 2-(1*H*-imidazol-1-
10 yl)ethanamine (50 mg, 0.45 mmol, *Synthetic Communications*
1991, 21, 535-544) and the mixture was stirred at ambient
temperature for 30 min. The mixture was diluted with
ethyl acetate and washed with saturated sodium
bicarbonate/water (4X), dried (sodium sulfate),
15 evaporated and purified by chromatography (silica gel,
dichloromethane/2M ethanolic ammonia, 93:7) to provide
the title compound as a white solid (25 mg). ¹H NMR (DMSO-
d₆): δ 0.78 (3H, d), 0.82 (3H, d), 1.2 (1H, dd), 1.4 (1H,
quintuplet), 1.9-2.0 (1H, m), 2.4 (1H, t), 2.55-2.80 (3H,
20 m), 2.9-3.0 (2H, m), 3.3-3.4 (3H, m), 3.5-3.6 (4H, m),
3.7 (1H, t), 3.8 (1H, dd), 4.03-4.07 (2H, m), 4.8 (1H,
dt), 5.05 (1H, d), 5.5 (1H, d), 6.18 (2H, s), 6.87 (1H,
s), 6.9 (2H, d), 7.05 (1H, d), 7.15 (1H, s), 7.2 (2H, d),
7.23 (1H, s), 7.25-7.30 (2H, m), 7.6 (1H, s), 7.8 (1H,
25 t); MS: 730 (MH⁺)

Example 97

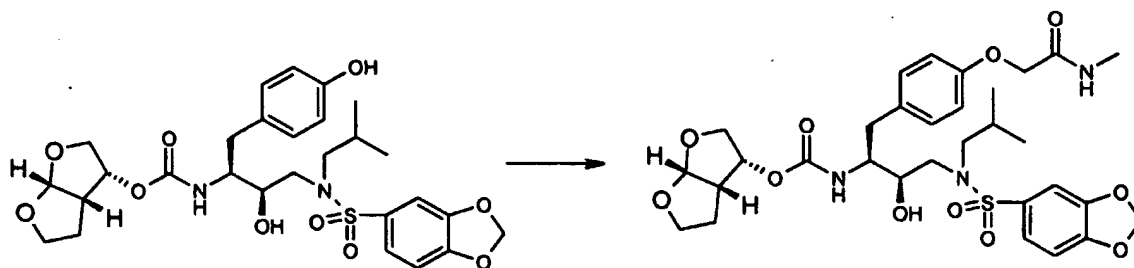
(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-[4-(2-amino-2-oxoethoxy)benzyl]-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxypropylcarbamate
 5 (314)



To a solution of (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-hydroxybenzyl)propylcarbamate (47 mg, 0.08 mmol) in anhydrous dimethylformamide (2 mL) was added cesium carbonate (78 mg, 0.24 mmol) and 2-bromoacetamide (22 mg, 0.16 mmol). After 1 h at ambient temperature, the mixture was diluted with ethyl acetate, washed with water (3X), brine, dried (sodium sulfate), and evaporated. The residue was purified by chromatography (silica gel, dichloromethane/methanol, 97:3) to afford the title product as a white solid (45 mg). ¹H NMR (DMSO-*d*₆): δ 0.78 (3H, d), 0.82 (3H, d), 1.2 (1H, dd), 1.4 (1H, quintuplet), 1.9-2.0 (1H, m), 2.35 (1H, t), 2.6-2.8 (3H, m), 2.9 (1H, d), 2.95 (1H, dd), 3.25-3.30 (1H, m), 3.45 (1H, br s), 3.5-3.6 (3H, m), 3.7 (1H, t), 3.8 (1H, dd), 4.3 (2H, s), 4.8 (1H, dt), 5.0 (1H, d), 5.5 (1H, d), 6.18 (2H, s), 6.8 (2H, d), 7.0-7.15 (3H, m), 7.22 (1H, s), 7.24 (1H, d), 7.26 (1H, d), 7.32 (1H, s), 7.42 (1H, s); MS: 650 (MH⁺)

Example 98

(3*R*,3*aS*,6*aR*) -Hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*) -3-
 [(1,3-benzodioxol-5-ylsulfonyl) (isobutyl) amino] -2-
 hydroxy-1-{4-[2-(methylamino)-2-oxoethoxy]benzyl}
 5 propylcarbamate (315)



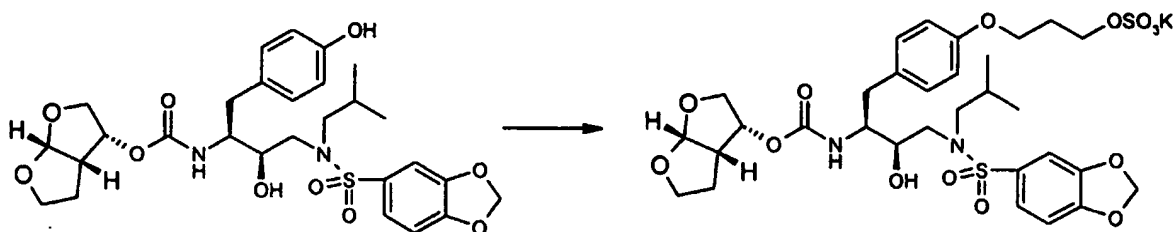
To a solution of (3*R*,3*aS*,6*aR*) -hexahydrofuro[2,3-*b*]furan-
 3-yl (1*S*,2*R*) -3-[(1,3-benzodioxol-5-
 10 ylsulfonyl) (isobutyl) amino] -2-hydroxy-1-(4-
 hydroxybenzyl)propylcarbamate (60 mg, 0.1 mmol) in
 anhydrous tetrahydrofuran (1.5 mL) was added 60% sodium
 hydride/mineral oil dispersion (4 mg, 0.1 mmol). The
 mixture was stirred for 10 min at ambient temperature
 15 under nitrogen atmosphere and a solution of *N*-methyl-2-
 bromoacetamide (17 mg, 0.11 mmol) in anhydrous
 tetrahydrofuran (0.5 mL) was added. After 2 h, an
 additional portion of 60% sodium hydride/mineral oil
 dispersion (4 mg, 0.1 mmol) was added. After 15 min,
 20 acetic acid (0.1 mL) was added and the mixture was
 diluted with ethyl acetate, washed with saturated sodium
 bicarbonate/water, dried (sodium sulfate), evaporated,
 and purified by chromatography (silica gel, ethyl
 acetate) to provide the title compound as a white solid
 25 (10 mg). ¹H NMR (DMSO-*d*₆): δ 0.78 (3H, d), 0.82 (3H, d),
 1.15-1.22 (1H, m), 1.2 (1H, quintuplet), 1.9-2.0 (1H,
 m), 2.35 (1H, t), 2.6 (3H, d), 2.65-2.80 (3H, m), 2.9

-225-

(1H, d), 2.95 (1H, dd), 3.2-3.3 (1H, m), 3.4-3.5 (1H, m),
 3.5-3.6 (3H, m), 3.7 (1H, t), 3.8 (1H, dd), 4.4 (2H, s),
 4.8 (1H, dt), 5.0 (1H, d), 5.5 (1H, d), 6.2 (2H, s), 6.8
 (2H, d), 7.0-7.2 (3H, m), 7.22 (1H, s), 7.25 (1H, d), 7.3
 5 (1H, d), 8.0 (1H, br s); MS: 664 (MH⁺);

Example 99

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 10 hydroxy-1-{4-[3-(sulfoxy)propoxy]benzyl}propylcarbamate
 Potassium Salt (316)



A mixture of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl
 (1S,2R)-3-[(1,3-benzodioxol-5-
 15 ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-
 hydroxybenzyl)propylcarbamate (35 mg, 0.06 mmol),
 potassium carbonate (8.1 mg, 0.06 mmol), 1,3,2-
 dioxathiane 2,2-dioxide (8.9 mg, 0.065 mmol, *J. Am. Chem.*
Soc. 1988, 110, 7538-7539) and acetonitrile was heated
 20 at 82°C under nitrogen atmosphere for 36 h and filtered
 while hot. The filtrate was allowed to cool to ambient
 temperature for 18 h and the resulting solid was filtered
 and washed with diethyl ether to provide the title
 compound as a white solid (25 mg). ¹H NMR (DMSO-d₆): δ
 25 0.78 (3H, d), 0.82 (3H, d), 1.25 (1H, dd), 1.4 (1H,
 quintuplet), 1.9-2.0 (3H, m), 2.2 (1H, t), 2.7-2.8 (3H,
 m), 2.9 (1H, d), 3.0 (1H, dd), 3.25-3.00 (1H, m), 3.4-3.5

-226-

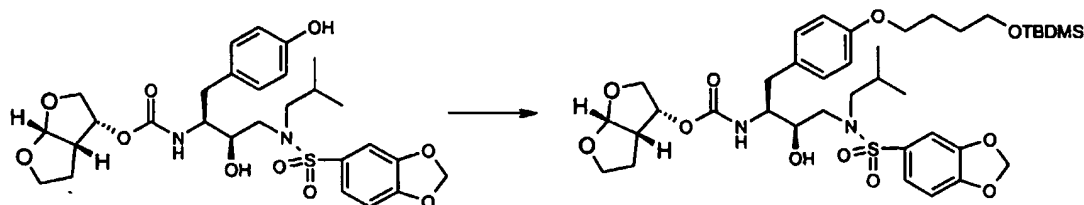
(1H, m), 3.50-3.65 (3H, m), 3.7 (1H, t), 3.75-3.82 (3H, m), 3.9 (1H, t), 4.08 (1H, dd), 4.8 (1H, dt), 4.97 (1H, d), 5.5 (1H, d), 6.18 (2H, s), 6.78 (2H, d), 7.0-7.1 (3H, m), 7.19 (1H, d), 7.20 (1H, s), 7.30 (1H, d); MS: 730

5 (MH⁺)

Example 100

Step 1:

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 10 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-(4-{
 {tert-butyl(dimethyl)silyl}oxy}butoxy)benzyl]-2-
 hydroxypropylcarbamate

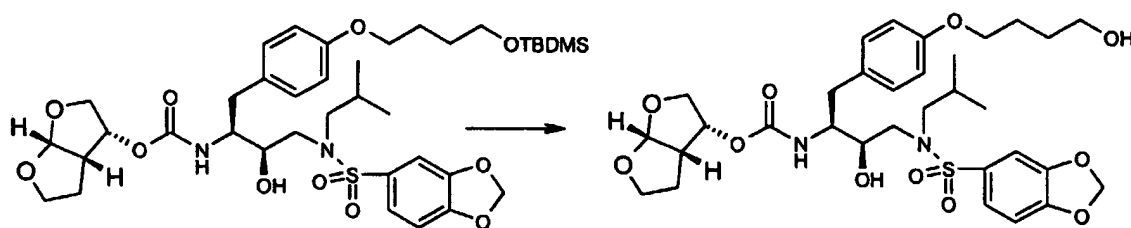


15 To a solution of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-hydroxybenzyl)propylcarbamate (0.6 g, 1.01 mmol), triphenyl phosphine (0.4 g, 1.52 mmol), and 4-{tert-butyl(dimethyl)silyl}oxy}-1-butanol (0.31 g, 1.52 mmol,
 20 *J. Org. Chem.* 1986, 51, 3388-3390) in anhydrous dichloromethane (9 mL) at 0°C under nitrogen atmosphere was slowly added a solution of diisopropyl azodicarboxylate (0.29 mL, 0.3 g, 1.52 mmol) in anhydrous
 25 dichloromethane (2 mL) and the mixture was stirred at ambient temperature for 2 h. Solvent was evaporated and the residue was purified by chromatography (silica gel,

hexanes/ethyl acetate, 1:1) to provide the title compound as a solid foam (0.39 g). ^1H NMR ($\text{DMSO}-d_6$): δ 0.0 (6H, s), 0.78 (3H, d), 0.80 (3H, d), 0.82 (9H, s), 1.22 (1H, dd), 1.4 (1H, quintuplet), 1.55 (2H, quintuplet), 1.7 (2H, quintuplet), 1.8-1.9 (1H, m), 2.35 (1H, t), 2.65-2.80 (3H, m), 2.9 (1H, d), 3.0 (1H, dd), 3.2-3.3 (2H, m), 3.4-3.5 (1H, m), 3.52-3.62 (4H, m), 3.7 (1H, t), 3.8 (1H, dd), 3.9 (2H, t), 4.8 (1H, dt), 5.0 (1H, br s), 5.5 (1H, d), 6.18 (2H, s), 6.77 (2H, d), 7.0-7.1 (3H, m), 7.19 (1H, d), 7.21 (1H, s), 7.3 (1H, d); MS: 801 ($\text{M}+23$); $\text{C}_{38}\text{H}_{58}\text{N}_2\text{O}_{11}\text{Si}$.

Step2:

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-[4-(4-hydroxybutoxy)benzyl]propylcarbamate (317)



20

To a solution of (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-(4-{[tert-butyl(dimethyl)silyl]oxy}butoxy)benzyl]-2-hydroxypropylcarbamate (0.38 g, 0.48 mmol) in tetrahydrofuran (5 mL) at 0°C was added a 1:1 mixture of 1M tetra-*n*-butyl ammonium fluoride/tetrahydrofuran and acetic acid (1.2 mL) and the mixture was stirred at

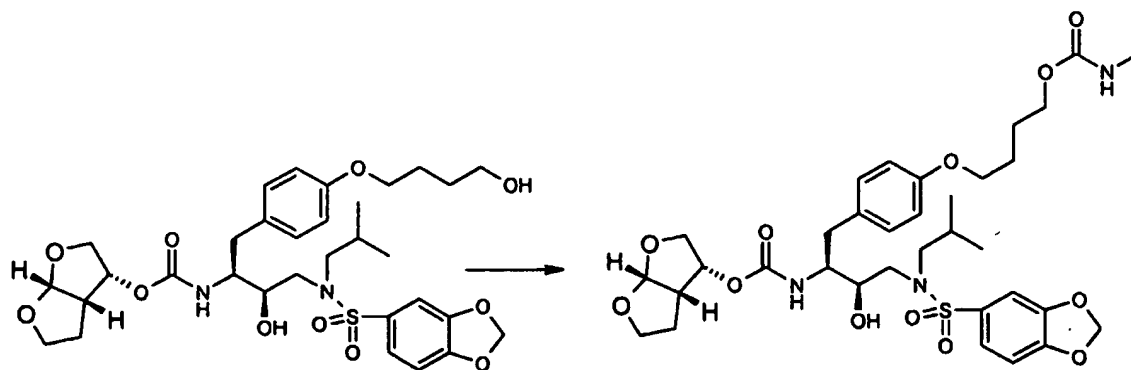
25

ambient temperature for 18 h. The mixture was diluted with ethyl acetate and washed with water (4X), dried (sodium sulfate) and evaporated. The resulting solid was triturated with diethyl ether and filtered to afford the
 5 title compound as a white solid (0.24 g). ¹H NMR (DMSO-
_d₆): δ 0.78 (3H, d), 0.82 (3H, d), 1.2 (1H, dd), 1.38 (1H, quintuplet), 1.5 (2H, quintuplet), 1.65 (2H, quintuplet), 1.9-2.0 (1H, m), 2.18 (1H, t), 2.7-2.8 (3H, m), 2.9 (1H, d), 2.97 (1H, dd), 3.20-3.25 (1H, m), 3.38 (2H, t), 3.4-
 10 3.5 (1H, m), 3.52-3.62 (3H, m), 3.7 (1H, t), 3.8 (1H, dd), 3.93 (2H, t), 4.2 (1H, br s), 4.8 (1H, dt), 5.0 (1H, d), 5.5 (1H, d), 6.18 (2H, s), 6.78 (2H, d), 7.0-7.1 (3H, m), 7.2 (1H, d), 7.26 (1H, s), 7.3 (1H, d); MS: 665 (MH⁺)

15

Example 101

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(4-{[(methylamino)carbonyl]oxy}butoxy)
 20 benzyl]propylcarbamate (318)



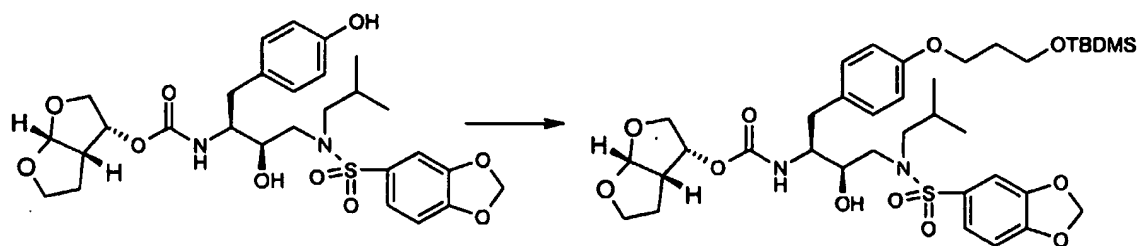
(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 25 hydroxy-1-[4-(4-hydroxybutoxy)benzyl]propylcarbamate was

treated with methyl isocyanate/dichloromethane as described earlier to afford the title compound as a solid foam. ¹H NMR (DMSO-*d*₆): δ 0.78 (3H, d), 0.82 (3H, d), 1.2 (1H, dd), 1.4 (1H, quintuplet), 1.6-1.8 (4H, m), 1.9-2.0 (1H, m), 2.38 (1H, t), 2.5 (3H, d), 2.7-2.8 (3H, m), 2.9 (1H, d), 2.98 (1H, dd), 3.3-3.4 (1H, m), 3.4-3.5 (1H, m), 3.5-3.6 (3H, m), 3.7 (1H, t), 3.8 (1H, dd), 3.9 (2H, t), 3.95 (2H, t), 4.8 (1H, dt), 5.0 (1H, br s), 5.5 (1H, d), 6.18 (2H, s), 6.78 (2H, d), 6.9 (1H, br s), 7.0-7.1 (3H, m), 7.2 (1H, d), 7.25 (1H, s), 7.3 (1H, d); MS: 744 (M+23); C₃₄H₄₇N₃O₁₂S.

Example 102

Step 1:

(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-(3-{[*tert*-butyl(dimethyl)silyl]oxy}propoxy)benzyl]-2-hydroxypropylcarbamate



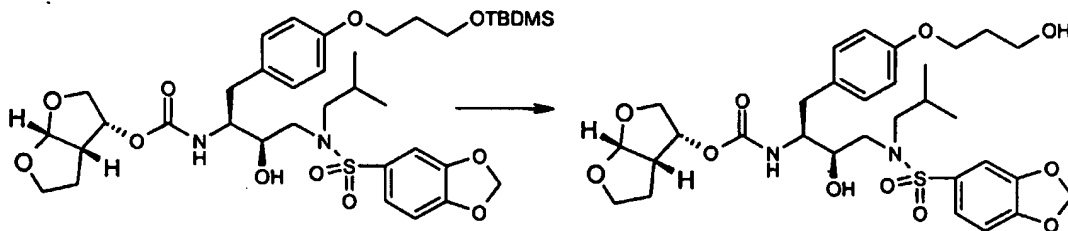
(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-hydroxybenzyl)propylcarbamate was treated with 3-{[*tert*-butyl(dimethyl)silyl]oxy}-1-propanol (*J. Org. Chem.* 1986, 51, 3388-3390)/triphenyl phosphine/diisopropyl azodicarboxylate as described in

-230-

step a (Example 213) to provide the title compound as solid foam. ^1H NMR ($\text{DMSO}-d_6$): δ 0.0 (6H, s), 0.78 (3H, d), 0.8 (9H, s), 0.82 (3H, d), 1.2 (1H, dd), 1.4 (1H, quintuplet), 1.8 (2H, quintuplet), 1.9-2.0 (1H, m), 2.38 (1H, dd), 2.6-2.8 (3H, m), 2.9 (1H, d), 2.98 (1H, dd), 3.2-3.3 (2H, m), 3.35-3.45 (1H, m), 3.5-3.6 (3H, m), 3.7 (2H, t), 3.8 (1H, dd), 3.9 (2H, t), 4.8 (1H, dt), 5.0 (1H, d), 5.5 (1H, d), 6.18 (2H, s), 6.75 (2H, d), 7.0-7.1 (3H, m), 7.18 (1H, d), 7.2 (1H, s), 7.28 (1H, d); MS: 765 (MH⁺)

Step 2:

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-[4-(3-hydroxypropoxy)benzyl]propylcarbamate (319)



(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-(3-{[tert-butyl(dimethyl)silyl]oxy}propoxy)benzyl]-2-hydroxypropylcarbamate was treated with 1M tetra-n-butyl ammonium fluoride/tetrahydrofuran/acetic acid as described in step b (Example 213) to afford the title compound as a white solid. ^1H NMR ($\text{DMSO}-d_6$): δ 0.78 (3H, d), 0.82 (3H, d), 1.2 (1H, dd), 1.38 (1H, quintuplet), 1.8 (2H, quintuplet), 1.9-2.0 (1H, m), 2.38 (1H, t), 2.6-

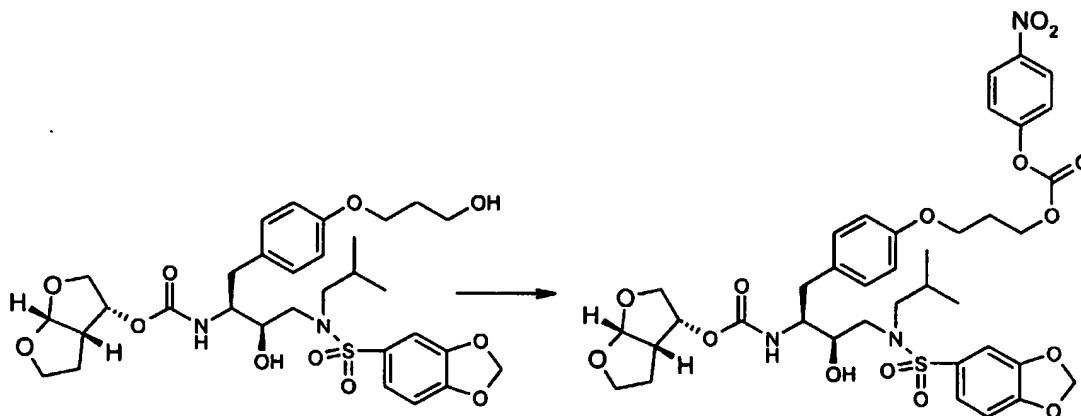
-231-

2.8 (3H, m), 2.9 (1H, d), 2.96 (1H, dd), 3.3 (1H, br s),
 3.4-3.6 (6H, m), 3.7 (1H, t), 3.8 (1H, dd), 3.9 (2H, t),
 4.5 (1H, t), 4.8 (1H, dt), 5.0 (1H, d), 5.5 (1H, d), 6.18
 (2H, s), 6.78 (2H, d), 7.0-7.1 (3H, m), 7.2 (1H, d), 7.25
 5 (1H, s), 7.3 (1H, d); MS: 651 (MH⁺)

Example 103

Step 1:

10 3-(4-{(2*S*,3*R*)-2-({[(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-
b]furan-3-yloxy]carbonyl}amino)-4-[(1,3-benzodioxol-5-
 ylsulfonyl)(isobutyl)amino]-3-hydroxybutyl}phenoxy)propyl
 4-nitrophenyl carbonate



15

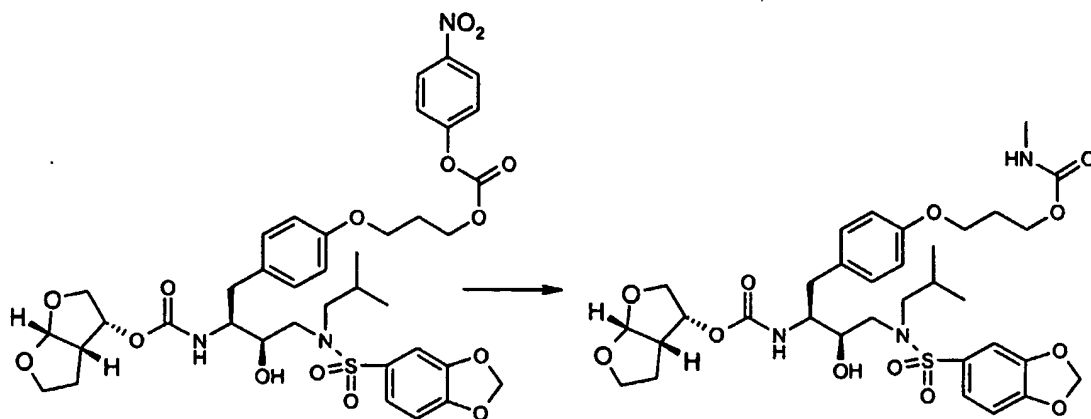
(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(3-hydroxypropoxy)benzyl]propylcarbamate was
 20 treated with 4-nitrophenyl chloroformate as described
 previously to provide the title compound as a solid foam.
¹H NMR (DMSO-*d*₆): δ 0.86 (3H, d), 0.92 (3H, d), 1.2 (1H,
 dd), 1.38 (1H, quintuplet), 1.9-2.0 (1H, m), 2.05-2.15

-232-

(2H, m), 2.2 (1H, t), 2.6-2.8 (3H, m), 2.9 (1H, d), 2.96 (1H, dd), 3.2-3.3 (2H, m), 3.4-3.5 (1H, m), 3.5-3.6 (2H, m), 3.7 (1H, t), 3.8 (1H, dd), 4.0 (2H, t), 4.37 (2H, t), 4.8 (1H, dt), 5.0 (1H, d), 5.45 (1H, d), 6.18 (2H, s),
 5 6.78 (2H, d), 7.0-7.1 (3H, m), 7.20-7.25 (2H, m), 7.3 (1H, dd), 7.56 (2H, d), 8.25 (2H, d); MS: 816 (MH⁺)

Step 2:

10 (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(3-{[(methylamino)carbonyl]oxy}propoxy)
 benzyl]propylcarbamate (320)



15

3-(4-{(2S,3R)-2-({[(3R,3aS,6aR)-Hexahydrofuro[2,3-
 b]furan-3-yloxy]carbonyl}amino)-4-[(1,3-benzodioxol-5-
 ylsulfonyl)(isobutyl)amino]-3-hydroxybutyl}phenoxy)propyl
 4-nitrophenyl carbonate was treated with 2M

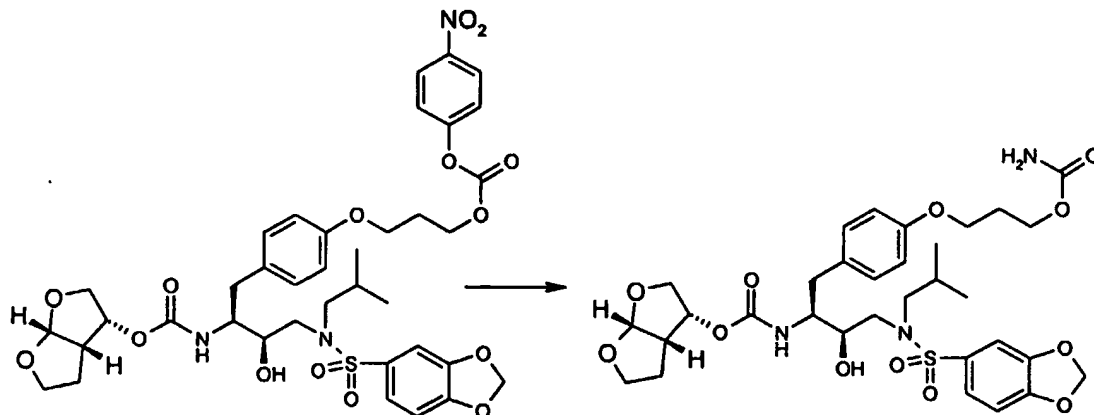
20 methylamine/tetrahydrofuran as described above to provide
 the title compound as a white solid. ¹H NMR (DMSO-d₆): δ
 0.78 (3H, d), 0.84 (3H, d), 1.1-1.2 (1H, m), 1.2 (1H, br
 quintuplet), 1.9-2.0 (3H, m), 2.17 (1H, t), 2.45 (3H, d),

-233-

2.6-2.8 (3H, m), 2.83-3.00 (2H, m), 3.4-3.6 (5H, m), 3.7 (1H, br s), 3.8 (1H, br s), 3.9 (2H, br s), 4.0 (2H, br s), 4.8-4.9 (1H, m), 5.0 (1H, d), 5.5 (1H, d), 6.17 (2H, s), 6.7-6.8 (2H, m), 6.9 (1H, br s), 7.0-7.1 (3H, m),
 5 7.2-7.4 (3H, m); MS: 708 (MH⁺);

Example 104

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-(4-
 10 {3-[(aminocarbonyl)oxy]propoxy}benzyl)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxypropylcarbamate (321)



15 3-(4-((2S,3R)-2-({[(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yloxy}carbonyl)amino)-4-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-3-hydroxybutyl}phenoxy)propyl
 4-nitrophenyl carbonate was treated with concentrated ammonium hydroxide as described above to afford the title
 20 compound as a white solid. ¹H NMR (DMSO-d₆): δ 0.78 (3H, d), 0.82 (3H, d), 1.2-1.3 (1H, m), 1.4 (1H, quintuplet), 1.9-2.0 (3H, m), 2.2 (1H, t), 2.6-2.8 (3H, m), 2.9 (1H, d), 2.97 (1H, dd), 3.2-3.3 (1H, m), 3.4-3.6 (4H, m), 3.7 (1H, t), 3.8 (1H, dd), 3.9 (2H, t), 4.0 (2H, t), 4.8 (1H,

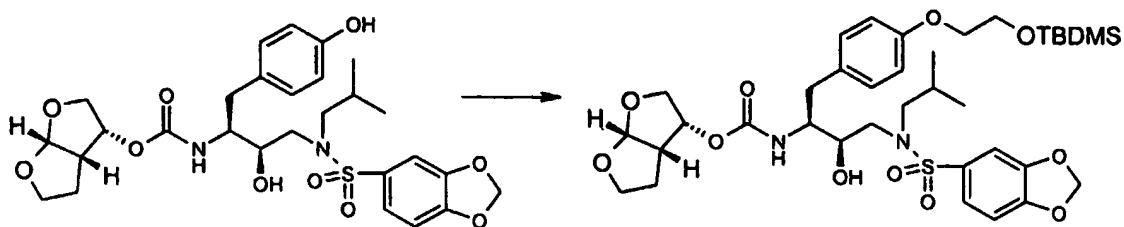
dt), 5.0 (1H, d), 5.5 (1H, d), 6.17 (2H, s), 6.4 (2H, br s), 6.78 (2H, d), 7.0-7.1 (3H, m), 7.2-7.3 (3H, m); MS: 694 (MH⁺)

5

Example 105

Step 1:

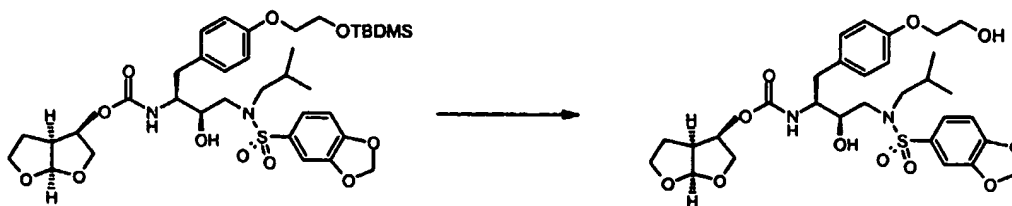
(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-(1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-(2-
 10 { [tert-butyl(dimethyl)silyl]oxy}ethoxy)benzyl]-2-
 hydroxypropylcarbamate



(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 15 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-(4-hydroxybenzyl)propylcarbamate was treated
 with 2-{[tert-butyl(dimethyl)silyl]oxy}-1-ethanol (*J.*
Org. Chem. **1986**, *51*, 3388-3390)/triphenyl
 phosphine/diisopropyl azodicarboxylate as described above
 20 to provide the title compound as solid foam. ¹H NMR (DMSO-
 d₆): 0.0 (6H, s), 0.78 (3H, d), 0.82 (3H, d), 0.84 (9H,
 s), 1.2 (1H, dd), 1.37 (1H, quintuplet), 1.9-2.0 (1H, m),
 2.37 (1H, dd), 2.6-2.8 (2H, m), 2.9 (1H, d), 2.98 (1H,
 dd), 3.2-3.3 (1H m), 3.4-3.5 (1H, m), 3.5-3.6 (4H, m),
 25 3.7 (1H, t), 3.8 (1H, dd), 3.88 (2H, dd), 3.93 (2H, dd),
 4.8 (1H, dt), 5.0 (1H, d), 5.45 (1H, d), 6.18 (2H, s),
 6.78 (2H, d), 7.0-7.1 (3H, m), 7.18 (1H, d), 7.2 (1H, s),
 7.28 (1H, d); MS: 751 (MH⁺)

Step 2:

(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 5 hydroxy-1-[4-(2-hydroxyethoxy)benzyl]propylcarbamate
 (322)



10

To a stirred solution of (3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-yl-(1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-(2-{[tert-butyl(dimethyl)silyl]oxy}ethoxy)benzyl]-2-

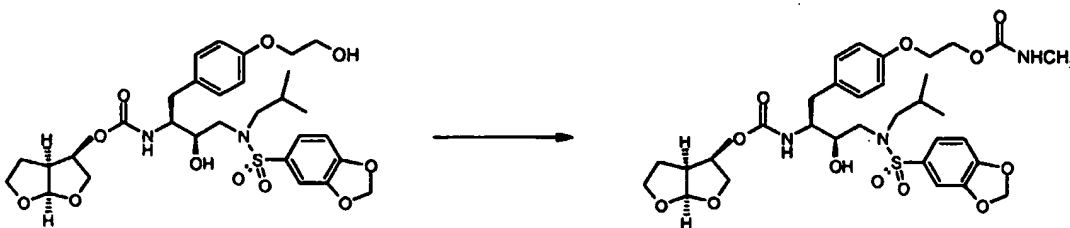
15 hydroxypropylcarbamate (160mg, 0.21 mmol) in tetrahydrofuran (3 mL) at 5 °C was added a mixture of tetrabutylammonium fluoride (0.3 mL, 1M in tetrahydrofuran) and glacial acetic acid (0.3 mL) over 2 minutes. The reaction was allowed to warm to ambient
 20 temperature and stirred for 18 hours. The mixture was diluted with ethyl acetate (50 mL), washed with water (25 mL) followed by saturated sodium bicarbonate (20 mL) and then brine (20 mL), dried (magnesium sulfate) and concentrated *in vacuo* to afford the title compound (135
 25 mg, quant.) as a white solid. ¹H NMR (DMSO-*d*₆): δ 0.78 (6H, dd), 1.17-1.42 (2H, m), 1.92 (1H, m), 2.33 (1H, t), 2.64-2.78 (3H, m), 2.89-3.02 (2H, m), 3.24-3.29 (1H, m), 3.52-3.73 (7H, m), 3.78-3.82 (1H, m), 3.86 (2H, t), 4.78-

-236-

4.82 (2H, m), 4.99 (1H, d), 5.46 (1H, d), 6.12 (2H, s),
6.73 (2H, d), 7.02-7.28 (6H, m); MS: 637 (MH⁺)

Example 106

- 5 (3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
hydroxy-1-[4-(2-{[(methylamino)carbonyl]oxy}ethoxy)
benzyl]propylcarbamate (323)



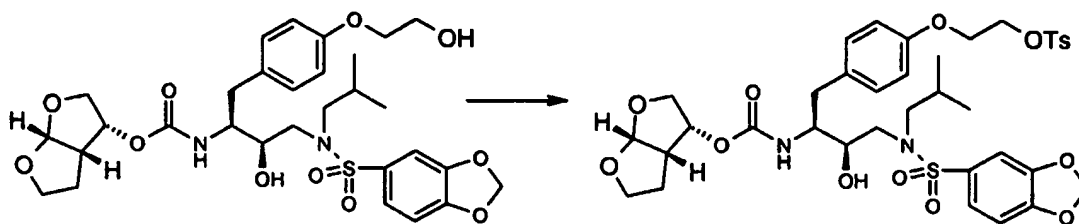
- 10 Treatment of (3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-yl
(1*S*,2*R*)-3-[(1,3-benzodioxol-5-
ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-[4-(2-
hydroxyethoxy)benzyl]propylcarbamate with methyl
15 isocyanate in dichloromethane as described earlier
afforded the title compound as a white foam in 52% yield.
¹H NMR (DMSO-*d*₆): δ 0.78 (6H, dd), 1.17-1.42 (2H, m), 1.92
(1H, m), 2.33 (1H, t), 2.60 (3H, d), 2.64-2.78 (3H, m),
2.88-2.98 (2H, m), 3.24-3.29 (1H, m), 3.40-3.60 (4H, m),
3.70 (1H, t), 3.78-3.82 (1H, m), 3.97-4.04 (2H, m), 4.19
20 (2H, t), 4.80 (1H, q), 4.99 (1H, d), 5.46 (1H, d), 6.12
(2H, d), 6.74 (2H, d), 7.02-7.28 (6H, m), 8.07 (1H, m);
MS: 694 (MH⁺)

Example 107

- 25 Step 1:

-237-

2- (4- { (2*S*, 3*R*) -2- ({ [(3*R*, 3*aS*, 6*aR*) -Hexahydrofuro [2, 3-
b] furan-3-yloxy] carbonyl} amino) -4- [(1, 3-benzodioxol-5-
 ylsulfonyl) (isobutyl) amino] -3-hydroxybutyl} phenoxy) ethyl
 4-methylbenzenesulfonate

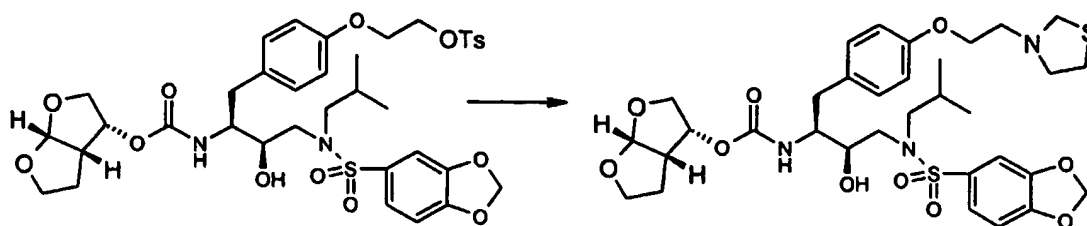


5

To a solution of (3*R*, 3*aS*, 6*aR*) -Hexahydrofuro [2, 3-*b*] furan-
 3-yl (1*S*, 2*R*) -3- [(1, 3-benzodioxol-5-
 ylsulfonyl) (isobutyl) amino] -2-hydroxy-1- [4- (2-
 10 hydroxyethoxy) benzyl] propylcarbamate (0.11 g, 0.18 mmol),
 triethyl amine (0.055 mL, 40 mg, 0.39 mmol), and 4-
 dimethylaminopyridine (2 mg), in dichloromethane at 0°C
 was added *p*-toluenesulfonyl chloride (38 mg, 0.2 mmol)
 and the mixture was stirred at ambient temperature for 4
 15 h. Solvent was evaporated and the residue was purified by
 chromatography (silica gel, dichloromethane/methanol,
 98:2) to provide the title compound as a solid foam
 (0.105 g). ¹H NMR (DMSO-*d*₆): δ 0.78 (3H, d), 0.82 (3H, d),
 1.2 (1H, dd), 1.37 (1H, quintuplet), 1.9-2.0 (1H, m), 2.3
 20 (1H, dd), 2.38 (3H, s), 2.6-2.8 (2H, m), 2.9 (1H, d),
 2.97 (1H, dd), 3.2-3.3 (1H, m), 3.4-3.5 (1H, m), 3.5-3.6
 (4H, m), 3.7 (1H, t), 3.8 (1H, dd), 4.0 (2H, d), 4.3 (2H,
 t), 4.8 (1H, dt), 5.0 (1H, d), 5.5 (1H, d), 6.18 (2H, s),
 6.7 (2H, d), 7.0-7.1 (3H, m), 7.2 (1H, d), 7.22 (1H, s),
 25 7.29 (1H, d), 7.4 (2H, d), 7.8 (2H, d); MS: 791 (MH⁺)

Step 2:

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-{4-[2-(1,3-thiazolidin-3-yl)ethoxy]benzyl}
 propylcarbamate (324)



5

A mixture of 2-(4-{(2S,3R)-2-({[(3R,3aS,6aR)-
 Hexahydrofuro[2,3-b]furan-3-yloxy]carbonyl}amino)-4-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-3-
 10 hydroxybutyl}phenoxy)ethyl 4-methylbenzenesulfonate (50
 mg, 0.06 mmol), thiazolidine (0.02 mL, 0.02 g, 0.25 mmol)
 and dimethylsulfoxide (1 mL) was heated to 70 °C under
 nitrogen atmosphere for 2 h. The mixture was diluted with
 water and extracted with ethyl ether (2X). The organic
 15 phase was dried (sodium sulfate), evaporated, and the
 residue was purified by chromatography (silica gel,
 dichloromethane/methanol, 98:2) to provide the title
 compound (25 mg) as a solid foam. ¹H NMR (DMSO-d₆): δ 0.78
 (3H, d), 0.82 (3H, d), 1.2 (1H, dd), 1.4 (1H,
 20 quintuplet), 1.9-2.0 (1H, m), 2.3 (1H, dd), 2.6-2.8 (7H,
 m), 2.8-3.0 (5H, m), 3.4-3.6 (4H, m), 3.7 (1H, t), 3.8
 (1H, dd), 4.0 (2H, br s), 4.05 (2H, br s), 4.8 (1H, dt),
 5.0 (1H, d), 5.5 (1H, d), 6.18 (2H, s), 6.8 (2H, d), 7.0-
 7.1 (3H, d), 7.18 (1H, d), 7.2 (1H, s), 7.3 (1H, d); MS:
 25 708 (MH⁺)

Example 108

Step 1:

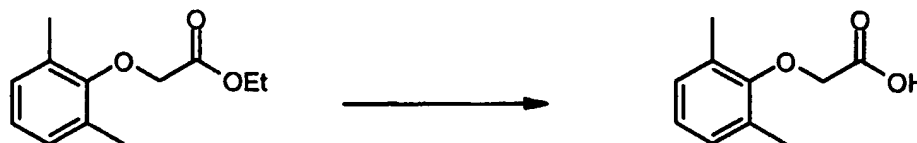
Ethyl 2',6'-dimethylphenoxyacetate

5



- 10 A mixture of 2,6-dimethylphenol (5.18 g, 42.4 mmol), potassium carbonate (7.33 g, 53.0 mmol) and ethyl bromoacetate (5.17 mL, 46.6 mmol) in acetone (40 mL) was stirred at ambient temperature for 24 hours. The reaction was filtered and the filtered solid was rinsed with
- 15 acetone. The filtrate was concentrated *in vacuo*, taken up in ethyl acetate (100 mL), washed with 0.1N sodium hydroxide (3 x 60 mL), dried (magnesium sulfate) and concentrated *in vacuo* to afford the crude title compound (8.79 g, quant.) as a pale yellow liquid. ¹H NMR (DMSO-
- 20 *d*₆): δ 1.17 (3H, t), 2.18 (6H, s), 4.14 (2H, q), 4.40 (2H, s), 6.86-6.98 (3H, m)

Step 2:

2',6'-Dimethylphenoxyacetic acid

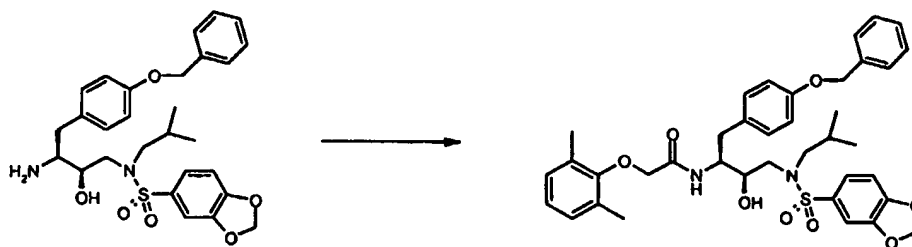
-240-

To an ice cold solution of ethyl 2',6'-dimethylphenoxyacetate (8.79 g, 42.4 mmol) in tetrahydrofuran/water (120 mL, 3:1) was added lithium hydroxide monohydrate (3.55 g, 84.8 mmol). After stirring
 5 for 3 hours at 5 °C, the tetrahydrofuran was removed in vacuo and the residual aqueous was diluted with water (70 mL) and extracted with ether (60 mL). The aqueous was then cooled in an ice bath and acidified to ~pH 2 with 1N hydrochloric acid. The resulting precipitate was
 10 extracted into ethyl acetate (150 mL), washed with water (50 mL), dried (magnesium sulfate) and concentrated in vacuo to afford the title compound (6.76g, 88%) as a white solid. ¹H NMR (CDCl₃) : δ 2.28 (6H,s), 4.46 (2H,s), 6.93-7.01 (3H, m), 10.25 (1H, broad)

15

Step 3:

N-{(1*S*,2*R*)-3-[(1,3-Benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-(benzyloxy)benzyl]-2-hydroxypropyl}-2-(2,6-
 20 dimethylphenoxy)acetamide (325)



To a stirred solution of *N*-{(2*R*,3*S*)-3-amino-4-[4-(benzyloxy)phenyl]-2-hydroxybutyl}-*N*-isobutyl-1,3-benzodioxole-5-sulfonamide (360 mg, 0.68 mmol), 2',6'-
 25 dimethylphenoxyacetic acid (160 mg, 0.89 mmol) and *N,N*-diisopropylethylamine (0.47 mL, 2.7 mmol) in acetonitrile (7 mL) was added

-241-

O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (390 mg, 1.0 mmol). After stirring at ambient temperature for 1.5 h, the reaction was concentrated *in vacuo*, taken up in ethyl acetate (60 mL), washed with 0.1N sodium hydroxide (3 x 50 mL) followed by brine (40 mL), dried (magnesium sulfate) and concentrated. The residue was purified by silica gel chromatography (60:40; hexane:ethyl acetate) to afford the title compound (450 mg, 95%) as a white foam. ¹H NMR (DMSO-d₆): δ 0.78 (6H, dd), 1.94 (1H, m), 2.09 (6H, s), 2.63 (1H, dd), 2.72 (1H, dd), 2.83 (1H, dd), 2.93-3.02 (2H, m), 3.28-3.35 (1H, m), 3.64-3.72 (1H, m), 3.88 (1H, d), 3.89-3.96 (1H, m), 4.06 (1H, d), 5.01 (2H, s), 5.07 (1H, d), 6.11 (2H, s), 6.82-7.12 (8H, m), 7.25-7.40 (7H, m), 7.86 (1H, d); MS: 689 (MH⁺); C₃₈H₄₄N₂O₈S.

Example 109

Ethyl (4-{(2*S*,3*R*)-2-({[(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yloxy]carbonyl}amino)-4-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-3-hydroxybutyl}phenoxy)acetate (326)



25

To a stirred mixture of (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-

-242-

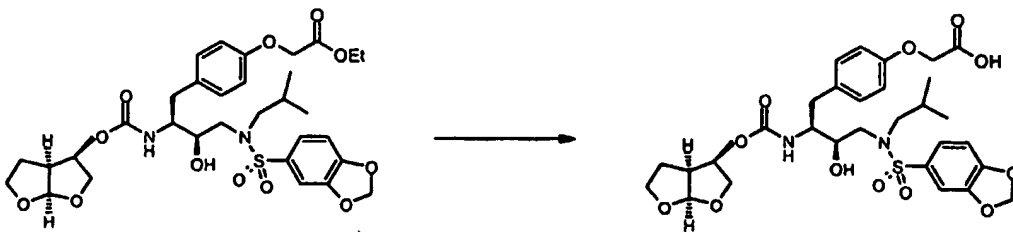
ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-hydroxybenzyl)propylcarbamate (200 mg, .34 mmol) and cesium carbonate (330 mg, 1.0 mmol) in N,N-dimethylformamide (5 mL) was added ethyl bromoacetate (75
 5 μ L, 0.67 mmol). After stirring at ambient temperature for 2 h, the reaction was diluted with ethyl acetate (50 mL), washed with water (3x40 mL), dried (magnesium sulfate) and concentrated in vacuo. The residue was purified by silica gel chromatography (60:40; ethyl acetate:hexane)
 10 to afford the title compound (162mg, 71%) as a white foam. ^1H NMR (DMSO- d_6): δ 0.78 (6H, dd), 1.16 (3H, t), 1.17-1.43 (2H, m), 1.92 (1H, m), 2.35 (1H, t), 2.64-2.78 (3H, m), 2.88-3.01 (2H, m), 3.24-3.29 (1H, m), 3.40-3.60 (4H, m), 3.70 (1H, t), 3.78-3.82 (1H, m), 4.10 (2H, q),
 15 4.65 (2H, s), 4.81 (1H, q), 5.00 (1H, d), 5.46 (1H, d), 6.12 (2H, s), 6.73 (2H, d), 7.02-7.07 (3H, m), 7.20-7.28 (3H, m); MS: 679 (MH^+)

Example 110

20

(4-{(2S,3R)-2-({[(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yloxy]carbonyl}amino)-4-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-3-hydroxybutyl}phenoxy)acetic acid (327)

25



-243-

To an ice cold solution of Ethyl (4-{(2*S*,3*R*)-2-
({[(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-
yloxy]carbonyl}amino)-4-[(1,3-benzodioxol-5-
ylsulfonyl)(isobutyl)amino]-3-
5 hydroxybutyl}phenoxy)acetate (107 mg, 0.16 mmol) in
tetrahydrofuran/water (4 mL, 3:1) was added lithium
hydroxide monohydrate (21 mg, 0.48 mmol). The reaction
was allowed to warm to ambient temperature and stir for 1
h. The tetrahydrofuran was evaporated and the residue
10 diluted with water (30 mL). The aqueous was then
extracted with ether (30 mL), cooled in an ice bath and
acidified to pH ~2 with 1.0 N hydrochloric acid. The
resulting precipitate was extracted into ethyl acetate
(30 mL), washed with water (20 mL), dried (magnesium
15 sulfate) and concentrated in vacuo to a white solid.
Triturated with 10% ether in hexane and filtered to
afford the title compound (77 mg) as a 2:1 mixture with
the compound derived from the loss of the bis-
tetrahydrofuran alcohol and subsequent ring closure at
20 the 2-hydroxy position. The mixture was confirmed by NMR,
HPLC and mass spectra. Data for major product: ¹H NMR
(DMSO-*d*₆): δ 0.78 (6H, dd), 1.17-1.45 (2H, m), 1.92 (1H,
m), 2.35 (1H, t), 2.64-2.78 (3H, m), 2.88-3.02 (2H, m),
3.24-3.30 (1H, m), 3.40-3.60 (4H, m), 3.70 (1H, t), 3.78-
25 3.82 (1H, m), 4.54 (2H, s), 4.82 (1H, q), 5.00 (1H, d),
5.46 (1H, d), 6.12 (2H, s), 6.71 (2H, d), 7.00-7.30 (6H,
m), 12.85 (1H, broad); MS: 651 (MH⁺); C₃₀H₃₈N₂O₁₂S (by-
product MS: 521 (MH⁺); C₂₄H₂₈N₂O₉S).

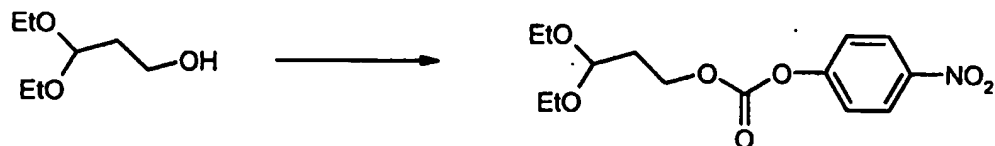
30

Example 328

Step 1:

3,3-Diethoxypropan-1-yl-4'-nitrophenyl carbonate

- 244 -

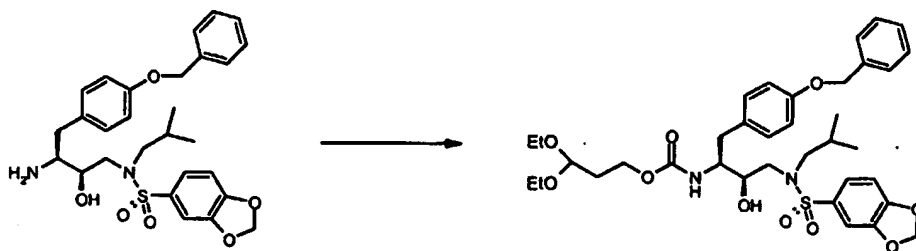


To an ice cold solution of 3,3-diethoxy-1-propanol (1.5 g, 10.1 mmol) and pyridine (1.0 mL, 12.2 mmol) in
 5 dichloromethane (30 mL) was added 4-nitrophenylchloroformate (2.24 g, 11.1 mmol). The reaction was allowed to warm to ambient temperature. After stirring for 18 h, the reaction was concentrated in vacuo, taken up in ethyl acetate (60 mL), washed with 5%
 10 aqueous citric acid (2x40 mL) followed by saturated sodium carbonate (3x40 mL), dried (magnesium sulfate) and concentrated. The residue was purified by silica gel chromatography (20% ethyl acetate in hexane) to afford the title compound (1.05g, 33%) as an oil. ¹H NMR
 15 (CDCl₃): δ 1.19 (6H, t), 2.05 (2H, q), 3.50 (2H, dq), 3.66 (2H, dq), 4.36 (2H, t), 4.66 (1H, t), 7.35 (2H, d), 8.25 (2H, d);

Step 2:

20

3,3-Diethoxypropyl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-(benzyloxy)benzyl]-2-hydroxypropylcarbamate (328)

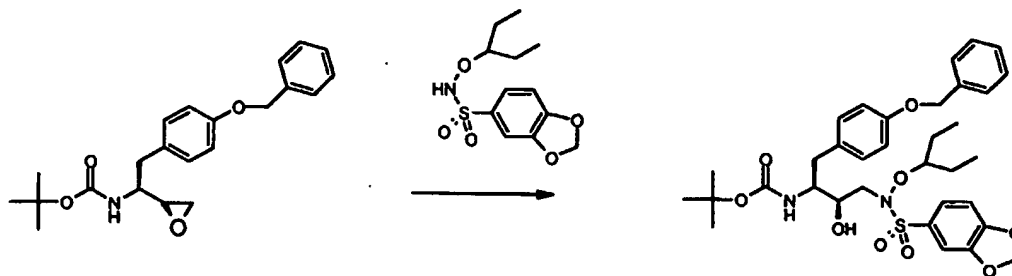


Treatment of *N*-{(2*R*,3*S*)-3-amino-4-[4-(benzyloxy)phenyl]-2-hydroxybutyl}-*N*-isobutyl-1,3-benzodioxole-5-sulfonamide with 3,3-diethoxypropan-1-yl-4'-nitrophenyl carbonate as described above provided the title compound as a white foam in 51% yield. ¹H NMR (DMSO-*d*₆): δ 0.78 (6H, dd), 1.33 (6H, dt), 1.65 (2H, q), 1.92 (1H, m), 2.46 (1H, t), 2.69-3.02 (4H, m), 3.27-3.58 (7H, m), 3.80 (2H, t), 4.43 (1H, t), 4.94 (1H, d), 4.99 (2H, s), 6.12 (2H, s), 6.83 (2H, d), 6.97 (1H, d), 7.03 (1H, d), 7.07 (2H, d), 7.23-7.39 (7H, m); MS: 701 (MH⁺)

Example 112

Step 1:

tert-Butyl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(1-ethylpropoxy)amino]-1-[4-(benzyloxy)benzyl]-2-hydroxypropylcarbamate

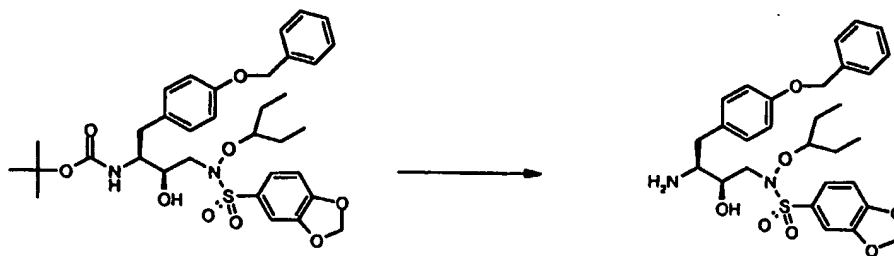


To a solution of *tert*-butyl (1*S*)-2-[4-(benzyloxy)phenyl]-1-[(2*S*)-oxiranyl]ethylcarbamate (2.66 g, 7.2 mmol) and the *N*-(1-ethylpropoxy)-1,3-benzodioxole-5-sulfonamide (2.30 g, 9.0 mmol) in tetrahydrofuran (12 mL) was added phosphazene base P4 *tert*-butyl solution (1.44 mL, 1.44 mmol, 1M in hexane). After stirring at ambient temperature for 18 h, the reaction was concentrated in vacuo, taken up in ethyl acetate (100 mL), washed with

0.5 N hydrochloric acid (2x40 mL) followed by water (40 mL), saturated sodium bicarbonate (40 mL) and brine (40 mL), dried (magnesium sulfate) and concentrated. The residue was purified by silica gel chromatography (20% ethyl acetate in hexane) to afford the title compound (4.25 g, 90%) as a white foam. ¹H NMR (DMSO-d₆): δ 0.79 (6H, dt), 1.11-1.74 (4H, m), 1.17 (9H, s), 2.37 (1H, t), 2.60-3.02 (3H, m), 3.38-3.49 (1H, m), 3.50-3.61 (1H, m), 4.03 (1H, m), 5.00 (2H, s), 5.04 (1H, d), 6.15 (2H, s), 6.60 (1H, d), 7.03 (2H, d), 7.10 (1H, d), 7.17-7.38 (9H, m)

Step 2:

***N*-{(2*R*,3*S*)-3-Amino-4-[4-(benzyloxy)phenyl]-2-hydroxybutyl}-*N*-(1-ethylpropoxy)-1,3-benzodioxole-5-sulfonamide**

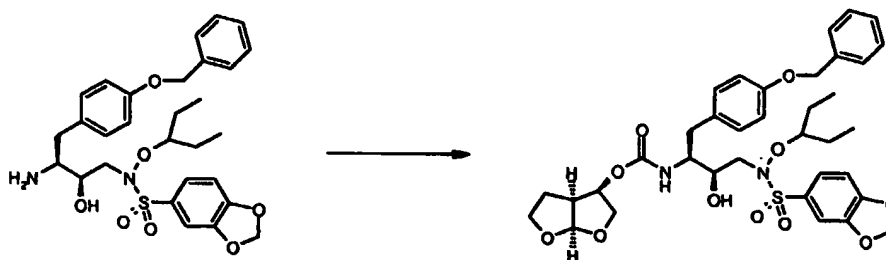


To an ice cold solution of tert-Butyl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(1-ethylpropoxy)amino]-1-[4-(benzyloxy)benzyl]-2-hydroxypropylcarbamate (1.5 g, 2.3 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (10 mL). After stirring at 5 °C for 3 h, the reaction was concentrated in vacuo, taken up in ethyl acetate (80 mL), washed with saturated sodium bicarbonate (2x50 mL), dried (magnesium sulfate) and concentrated in vacuo to afford the title compound (1.27

g, quant.) as an off-white foam. ^1H NMR ($\text{DMSO}-d_6$): δ 0.77 (6H, dt), 1.07-1.72 (4H, m), 1.82 (2H, br), 2.28 (1H, t), 2.58-3.05 (4H, m), 3.43-3.53 (1H, m), 3.95-4.03 (1H, m), 4.86 (1H, br s), 5.01 (2H, s), 6.16 (2H, s), 6.86 (2H, d), 7.03 (2H, d), 7.12-7.40 (8H, m);

Step 3:

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(1-ethylpropoxy)amino]-1-[4-(benzyloxy)benzyl]-2-hydroxypropylcarbamate (329)



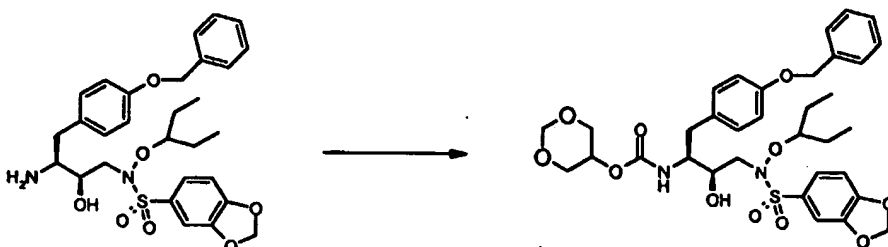
Treatment of *N*-{(2*R*,3*S*)-3-Amino-4-[4-(benzyloxy)phenyl]-2-hydroxybutyl}-*N*-(1-ethylpropoxy)-1,3-benzodioxole-5-sulfonamide with [(3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl][4-nitrophenyl] carbonate as described above provided the title compound as a white foam in 66% yield.

^1H NMR ($\text{DMSO}-d_6$): δ 0.82 (6H, t), 1.11-1.74 (6H, m), 2.32 (1H, t), 2.69-2.94 (4H, m), 3.45-3.66 (5H, m), 3.75-3.79 (1H, m), 3.99-4.03 (1H, m), 4.78 (1H, q), 5.00 (2H, s), 5.16 (1H, d), 5.46 (1H, d), 6.16 (2H, s), 6.82 (2H, d), 7.03 (2H, d), 7.11-7.38 (9H, m); MS: 713 (MH^+);

$\text{C}_{36}\text{H}_{44}\text{N}_2\text{O}_{11}\text{S}$.

Example 113

1,3-Dioxan-5-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(1-ethylpropoxy)amino]-1-[4-(benzyloxy)benzyl]-2-hydroxypropylcarbamate (330)

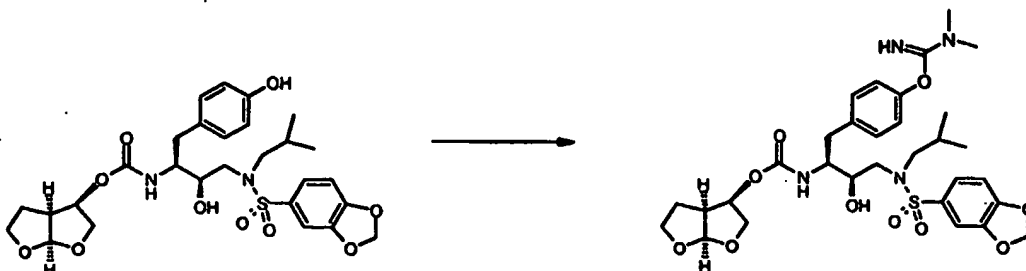


5 Treatment of *N*-{(2*R*,3*S*)-3-Amino-4-[4-(benzyloxy)phenyl]-2-hydroxybutyl}-*N*-(1-ethylpropoxy)-1,3-benzodioxole-5-sulfonamide with 1,3-dioxan-5-yl-4'-nitrophenyl carbonate as described earlier provided the title compound as a white foam in 65% yield. ¹H NMR (DMSO-*d*₆): δ 0.79 (6H, dt), 1.11-1.74 (4H, m), 2.39 (1H, t), 2.60-3.00 (3H, m), 3.45-3.63 (4H, m), 3.76-3.85 (2H, m), 4.02-4.04 (1H, m), 4.25 (1H, br s), 4.66 (1H, d), 4.74 (1H, d), 4.99 (2H, s), 5.09 (1H, d), 6.16 (2H, s), 6.82 (2H, d), 7.04 (2H, d), 7.12 (1H, d), 7.26-7.39 (7H, m); MS: 687 (MH⁺)

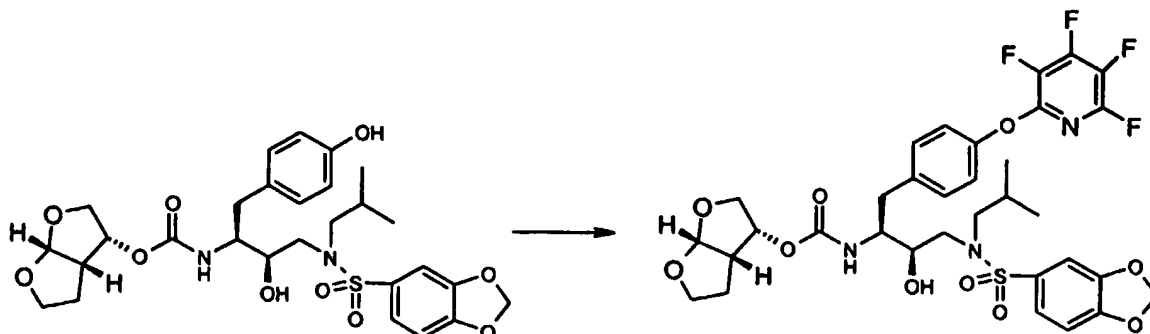
15

Example 114

(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-[(dimethylamino)(imino)methoxy]benzyl]-2-hydroxypropylcarbamate (331)

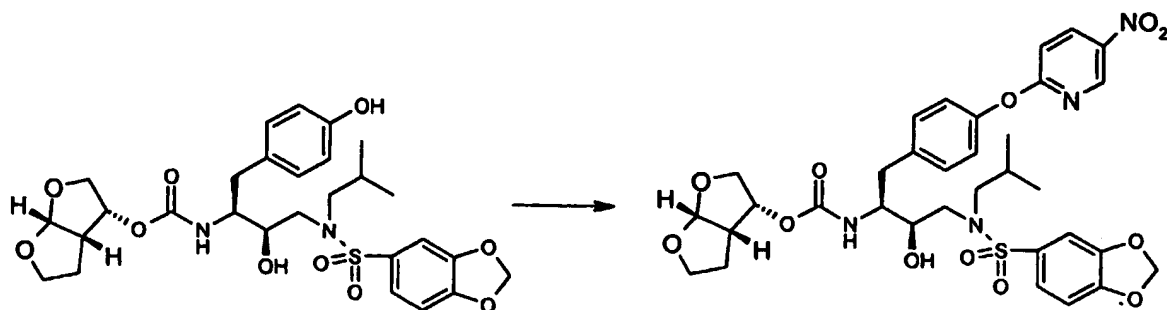


To an ice cold solution of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-hydroxybenzyl)propylcarbamate (100 mg, 0.17 mmol) and
5 cyanogen bromide (36 mg, 0.34 mmol) in acetone (2 mL) was added a solution of triethylamine (30 μ L, 0.21 mmol) in acetone (1 mL) over 1 h. After stirring at 5 $^{\circ}$ C for an additional 2 h, the reaction was concentrated in vacuo, taken up in ethyl acetate (40 mL), washed with water
10 (2x25 mL) followed by brine (25 mL), dried (magnesium sulfate) and concentrated to afford the crude cyanate (100 mg) as an oil. The cyanate was dissolved in fresh acetone (3 mL) and cooled to 5 $^{\circ}$ C. Dimethylamine (3 drops, 2 M in tetrahydrofuran) was added and the reaction was
15 stirred for 30 minutes. The acetone was evaporated and the residue was purified by silica gel chromatography (90:10:2; chloroform:methanol:ammonium hydroxide) to afford the title compound (45 mg, 40%) as a white solid.
 1 H NMR (DMSO- d_6): δ 0.78 (6H, dd), 1.18-1.45 (2H, m), 1.92
20 (1H, m), 2.44 (1H, t), 2.65-2.78 (3H, m), 2.86-3.02 (3H, m), 2.88 (6H, s), 3.24-3.29 (1H, m), 3.47-3.61 (4H, m), 3.69 (1H, t), 3.77-3.82 (1H, m), 4.82 (1H, q), 5.05 (1H, d), 5.47 (1H, d), 6.12 (2H, s), 6.95 (2H, d), 7.03 (1H, d), 7.17-7.31 (5H, m); MS: 663 (MH $^+$)

Example 115

5 (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-{4-[(3,4,5,6-tetrafluoro-2-pyridinyl)oxy]
 benzyl}propylcarbamate (332)

A mixture of 59mg (0.1 mmol) of (3R,3aS,6aR)-
 10 hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-
 benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-
 hydroxybenzyl)propylcarbamate, 51 mg (0.3 mMol) of
 pentafluoropyridine and 65mg (0.2 mMol) of cesium
 carbonate in 0.5 mL of dimethyl formamide was stirred at
 15 rt for 3h. The mixture was diluted with ethyl acetate
 and extracted with water. Evaporation of the solvent and
 chromatography on silica gel (1:1 ethyl acetate/ hexane)
 gave the title compound (32mg) as a white foam. ¹HNMR:
 0.85 (9H,dd), 1.55(1H,m), 1.65(1H,m), 1.8(1H,m),
 20 2.78(2H,m), 2.9-3.2(5H,m), 3.7(3H,m), 3.8(3H,m),
 3.95(1H,m), 4.95(2H,m), 5.62(1H,d), 6.04(2H,s),
 6.85(1H,d), 6.95(2H,d), 7.17(1H,s), 7.2(2H,d),
 7.34(1H,d). MS: 742 (M+H)

Example 116

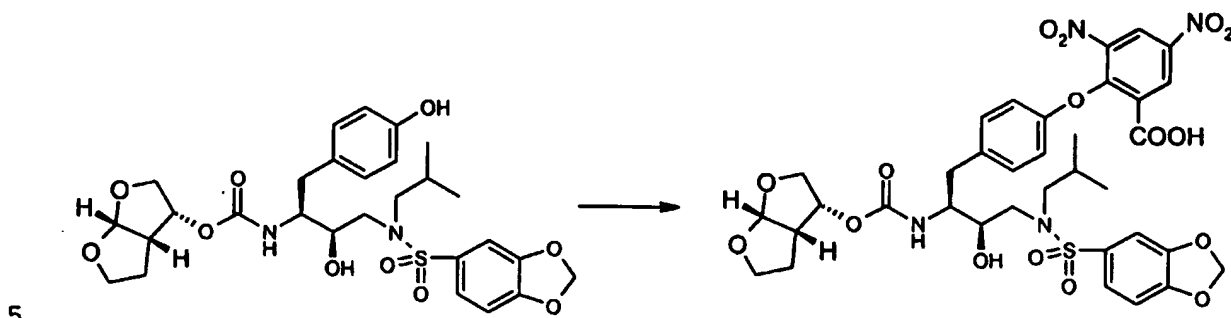
5

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-{4-[(5-nitro-2-pyridinyl)oxy]benzyl}

10 propylcarbamate (333)

A mixture of 59mg (0.1 mmol) of (3R,3aS,6aR)-
 hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-
 benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-
 hydroxybenzyl)propylcarbamate, 42 mg (0.3 mmol) of 2-
 15 chloro-5-nitropyridine and 65mg (0.2 mmol) of cesium
 carbonate in 0.5 mL of dimethyl formamide was stirred at
 rt for 12h. The mixture was diluted with ethyl acetate
 and extracted with water. Evaporation of the solvent and
 chromatography on silica gel (1:1 ethyl acetate/ hexane)
 20 gave the title compound (38mg) as a white foam.

¹H-NMR: 0.83 (6H, dd), 1.7 (2H, m), 1.8 (2H, m), 2.8-3.2 (7H, m),
 3.7 (3H, m), 3.8-4 (4H, m), 5.0 (2H, m), 5.62 (1H, d),
 6.03 (2H, s), 6.85 (1H, d), 6.97 (1H, d), 7.02 (2H, d),
 7.18 (1h, s), 7.35 (2H, d), 7.4 (1H, d), 8.42 (1H, d),
 25 8.90 (1H, d). MS: 715

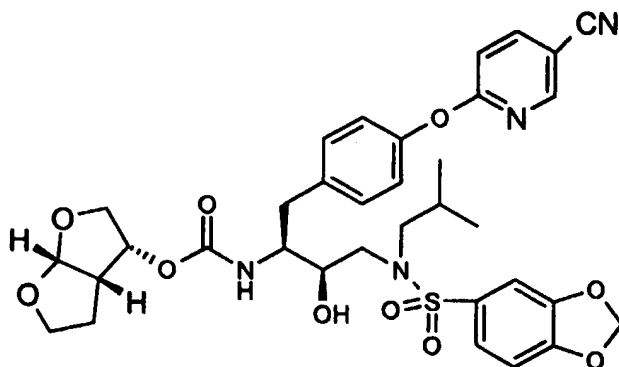
Example 117

2-(4-{(2*S*,3*R*)-2-({[(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-
b]furan-3-yl]oxy}carbonyl)amino)-4-[(1,3-benzodioxol-5-
ylsulfonyl)(isobutyl)amino]-3-hydroxybutyl}phenoxy)-3,5-
10 dinitrobenzoic acid (334)

A mixture of 59mg (0.1 mMol) of (3*R*,3*aS*,6*aR*)-
hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-
benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-
hydroxybenzyl)propylcarbamate, 50 of 2-fluoro-3,5-
15 dinitrobenzoic acid and 65mg (0.2 mMol) of cesium
carbonate in 0.5 mL of dimethyl formamide was stirred at
rt for 2h. The mixture was diluted with ethyl acetate
and extracted with 1*N* HCl. Evaporation of the solvent
and chromatography on silica gel (5% methanolic ammonia
20 in dichloromethane) gave the title compound (25mg) as a
yellow foam. ¹H NMR: 0.82(6H,dd), 1.42(1H,m), 1.63(1H,m),
1.90(2H,m), 2.46(1H,dd), 2.8(1H,dd), 2.82-3.02(5H,m),
3.2(1H,m), 3.6-3.95(6H,m), 4.94(1H,q), 5.58(1H,d),
6.02(2H,s), 6.61(1H,d), 6.75(2H,d), 6.82(1H,d),
25 7.05(2H,d), 7.3(1H,d), 7.45(1H,s), 8.6(2H,ss).

Example 118

5



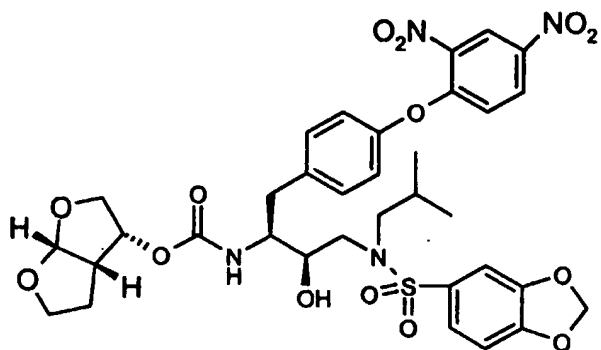
(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-{4-[(5-
10 cyano-2-pyridinyl)oxy]benzyl}-2-hydroxypropylcarbamate
(335)

A mixture of 59mg (0.1 mMol) of (3R,3aS,6aR)-
hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-
benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-
15 hydroxybenzyl)propylcarbamate, 120mg of 2-chloro-5-
cyanopyridine and 65mg (0.2 mMol) of cesium carbonate in
0.5 mL of dimethyl formamide was stirred at rt for 5h.
The mixture was diluted with ethyl acetate and extracted
with water. Evaporation of the solvent and
20 chromatography on silica gel (1:1 ethyl acetate- hexanes)
gave the title compound (16mg). ¹H NMR: 0.88(6H,dd),
1.55-1.8(3H,m), 2.8-3.2(7h,m), 3.65(2H,m), 3.8(2H,m),
3.95(1H,m), 5.0(2H,m), 5.6(1H,d), 6.05(2H,s), 6.82(1H,d),

6.95 (1H,d), 7.0 (2H,d), 7.1-7.4 (4H,m), 7.9 (1H,d),
8.4 (1H,bs). MS: 695 (M+H)

Example 119

5



(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
10 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-
(2,4-dinitrophenoxy)benzyl]-2-hydroxypropylcarbamate
(336)

A mixture of 100mg (0.17 mMol) of (3R,3aS,6aR)-
hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-
15 benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-
hydroxybenzyl)propylcarbamate, 24 mg of 2-chloro-5-
cyanopyridine and 27mg of triethylamine in 0.5 mL of
dimethyl formamide was stirred at rt for 5h. The mixture
was diluted with ethyl acetate and extracted with 1N HCl
20 and water. Evaporation of the solvent and chromatography
on silica gel (1:1 ethyl acetate- hexanes) gave the title
compound (140mg) as a yellow solid. ¹H NMR: 0.9(6H,dd),
1.6-1.8(3H,m), 2.8-3.2(9H,m), 3.7(3H,m), 3.8-4(4H,m),
5.0(2H,m), 5.6(1H,d), 6.05(2H,s), 6.85(1H,d), 6.99(1H,d),

7.05 (2H,d), 7.25 (1H,s), 7.3 (3H,m), 8.3 (1H,dd), 9.0 (1H,d).

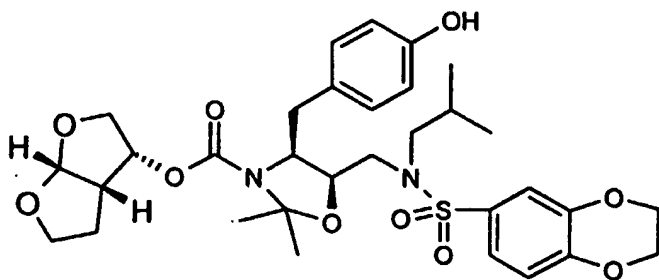
MS: 759 (M+H)

Example 120

5

Step 1:

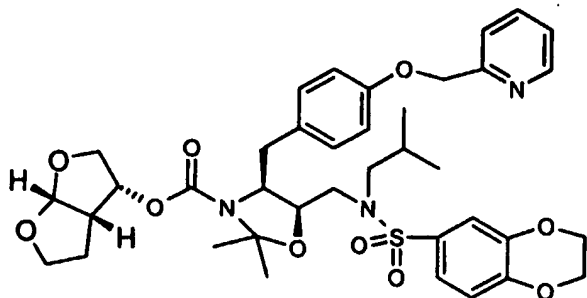
(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (4S,5R)-5-
 {[(2,3-dihydro-1,4-benzodioxin-6-
 10 ylsulfonyl)(isobutyl)amino]methyl}-4-(4-hydroxybenzyl)-
 2,2-dimethyl-1,3-oxazolidine-3-carboxylate



15 250mg of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl
 (1S,2R)-3-[(2,3-dihydro-1,4-benzodioxin-6-
 ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-
 benzyloxybenzyl)propylcarbamate, 2mL of 2,2-
 dimethoxypropane, 0.5g of p-toluenesulfonic acid in 50mL
 20 of dichloromethane were refluxed for 3h and then
 extracted with sodium bicarbonate solution.
 Chromatography on silica gel (1:1 ethylacetate/hexanes)
 gave 220mg of the desired compound as an oil which was
 dissolved in methanol and hydrogenated (at 50 psi) over
 25 5% palladium on carbon. Filtration and evaporation of
 the volatiles gave the desired title compound as an oil

Step 2:

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (4S,5R)-5-
 {[(2,3-dihydro-1,4-benzodioxin-6-
 5 ylsulfonyl)(isobutyl)amino]methyl}-2,2-dimethyl-4-[4-(2-
 pyridinylmethoxy)benzyl]-1,3-oxazolidine-3-carboxylate

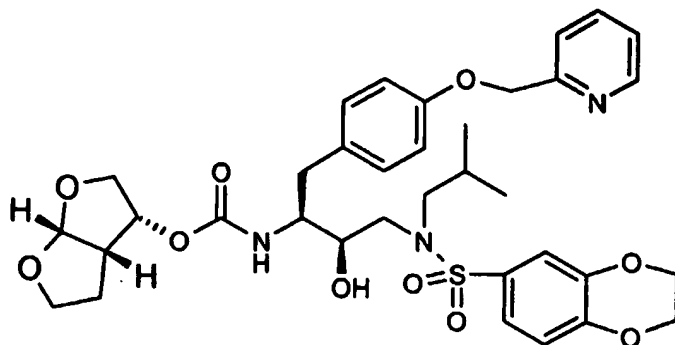


0.1g of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl
 10 (4S,5R)-5-{[(2,3-dihydro-1,4-benzodioxin-6-
 ylsulfonyl)(isobutyl)amino]methyl}-4-(4-hydroxybenzyl)-
 2,2-dimethyl-1,3-oxazolidine-3-carboxylate, 0.03g of o-
 picolylchloride-hydrochloride and 0.15g of cesium
 carbonate were suspended in 0.5 mL of dimethyl formamide
 15 and heated to 60 degrees for 3h. The mixture was diluted
 with ethyl acetate and washed with water. Chromatography
 on silica gel (9:1 ethyl acetate/hexanes) gave 72mg of
 the desired material

20 Step3:

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(2,3-dihydro-1,4-benzodioxin-6-
 ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-[4-(2-
 pyridinylmethoxy)benzyl]propylcarbamate (337)

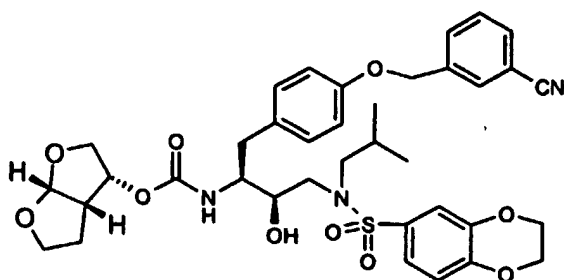
25



70mg of (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl
 (4*S*,5*R*)-5-{[(2,3-dihydro-1,4-benzodioxin-6-
 5 ylsulfonyl)(isobutyl)amino]methyl}-2,2-dimethyl-4-[4-(2-
 pyridinylmethoxy)benzyl]-1,3-oxazolidine-3-carboxylate
 were dissolved in 15mL of isopropanol and 5mL of
 concentrated hydrochloric acid. After 2h, the reaction
 was treated with excess 3N sodium hydroxide and extracted
 10 with ethyl acetate. Evaporation of the solvent gave 67mg
 of the desired product. ¹H NMR: 0.83(6H,dd), 1.4-
 1.8(4H,m), 2.6-3.2(7H,m), 3.6(2H,m), 3.75(2H,m),
 3.9(2H,m), 4.25(4H,bs), 4.95(1H,d), 5.0(1H,m), 5.6(1H,d),
 6.9(2H,d), 6.95(2H,d), 7.1(2H,d), 7.2(2H,m), 7.45(1H,d),
 15 7.7(1H,t), 8.58(1H,d).

Example 121

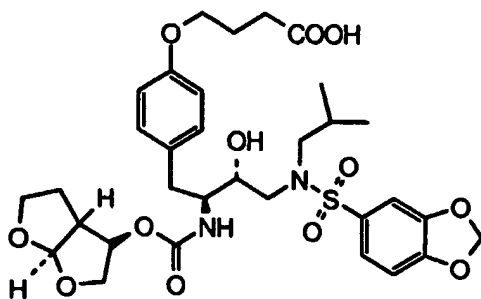
(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-{4-
 20 [(3-cyanobenzyl)oxy]benzyl}-3-[(2,3-dihydro-1,4-
 benzodioxin-6-ylsulfonyl)(isobutyl)amino]-2-
 hydroxypropylcarbamate (338)



49mg of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl
 (1S,2R)-3-[(2,3-dihydro-1,4-benzodioxin-6-
 ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-hydroxy
 5 benzyl)propylcarbamate, 20mg of m-cyanobenzylchloride,
 20mg of cesium carbonate and 0.5 mL of dimethyl formamide
 were stirred at rt for 5h. The mixture was diluted with
 ethyl acetate and extracted with water. Chromatography
 on silica gel (1:1 ethylacetate/hexane) gave the title
 10 compound as a white solid (26mg). ¹H NMR: 0.87(6H,dd),
 1.58(2H,m), 1.8(1H,m), 2.75(2H,m), 2.9(4H,m), 3.1(1H,m),
 3.62(3H,m), 3.8(3H,m), 3.95(1H,m), 4.25(4H,m),
 4.95(2H,m), 5.0(2H,s), 5.62(1H,d), 6.82(2H,d),
 6.92(1H,d), 7.1(2H,d), 7.2(2H,m), 7.45(1H,t), 7.6(2H,m),
 15 7.75(1H,s). MS:722 (M+H)

Example 122

4-(4-{(2S,3R)-2-({[(3R,3aS,6aR)-hexahydrofuro[2,3-
 b]furan-3-yloxy]carbonyl}amino)-4-[(1,3-benzodioxol-5-
 20 ylsulfonyl)(isobutyl)amino]-3-hydroxybutyl}phenoxy)
 butanoic acid (339)

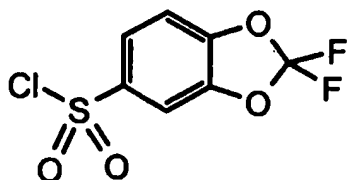


To a 0° C solution of Methyl 4-(4-{(2S,3R)-2-
({[3R,3aS,6aR]-hexahydrofuro[2,3-b]furan-3-
yloxy]carbonyl}amino)-4-[(1,3-benzodioxol-5-
5 ylsulfonyl)(isobutyl)amino]-3-
hydroxybutyl}phenoxy)butanoate (0.9 g, 0.144 mmol) in 8
ml of THF-H₂O (3:1) was added lithium hydroxide
monohydrate (30 mg, 0.715 mmol). The ice bath was removed
and the reaction mixture was stirred at room temperature
10 for 2 hours. Carefully acidified to pH 2 with 1N HCl and
diluted with 50 ml of dichloromethane. The organic layer
was washed with water and then dried with sodium sulfate,
filtered and concentrated under reduced pressure.
Residue was triturated with diethyl ether and filtered to
15 afford 85 mg (87%) of the title compound.
¹H-NMR: (DMSO-d₆): δ 0.79 (3H,d), 0.83 (3H,d), 1.20-1.31
(2H,m), 1.35-1.45 (2H,m) 1.80-1.98 (3H,m), 2.30-2.41
(2H,m), 2.65-2.82 (3H,m), 2.85-3.06 (3H,m), 3.34-3.61
(4H,m), 3.70-3.76 (1H,m), 3.82-3.98 (3H,m), 4.84 (1H,q),
20 5.01 (1H,d), 5.51 (1H,d), 6.17 (2H,s), 6.77 (2H,d), 6.88
(1H,d), 7.01-7.18 (3H,m), 7.23 (1H,d), 12.06 (1H,br s).
MS: 679 (M⁺). C₃₂H₄₂N₂O₁₂S.

Example 123

25 Step 1:

2,2-difluoro-1,3-benzodioxole-5-sulfonyl chloride

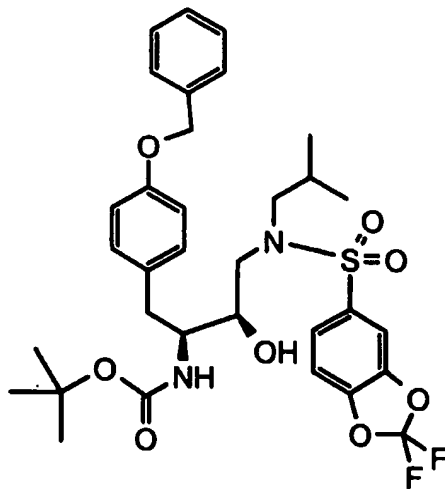


A solution of 2.37 g (10 mmol) 5-bromo-2,2-difluoro-1,3-benzodioxole in 25 ml anhydrous ether, cooled to -30 °C, and 4 ml (10 mmol) n butyllithium (2.5 M in hexanes) was added at -30 °C, over 10 minutes. The mixture was stirred at -30 °C for 1 hour, then sulfur dioxide gas was passed through the mixture at -20 °C for 5 minutes. The mixture then was allowed to warm up to 20 °C, and the precipitate was filtered and washed with 20 ml hexane. The solid was suspended in 20 ml hexanes, 1.35 g (10 mmol) sulfonyl chloride was added, the mixture was stirred at 20 °C for 48 hours. The mixture then was filtered and the filtrate was concentrated under reduced pressure to obtain 1.6 g (62 %) title compound. The product was used in the next step without further purification.

¹H-NMR (CDCl₃): δ 7.27 (1H,d), 7.74 (1H,s), 7.88 (1H,d).

Step 2:

tert-butyl (1S,2R)-1-[4-(benzyloxy)benzyl]-3-[[[(2,2-difluoro-1,3-benzodioxol-5-yl)sulfonyl](isobutyl)amino]-2-hydroxypropylcarbamate



The sulfonamide formation was carried out as described for t-Butyl-N((1S,2R)-1-(4-benzyloxy-benzyl)-3-i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl)-carbamate. (Y=73%)

5

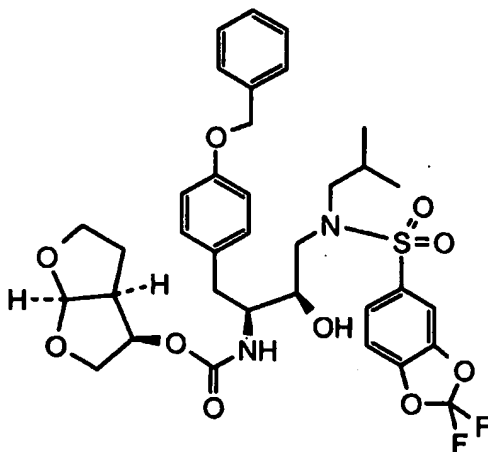
¹H-NMR (CDCl₃): δ 0.86 (3H,d), 0.88 (3H,d), 1.34 (9H,s), 1.84 (1H,m), 2.85 (4H,m), 3.09 (2H,d), 3.68 (1H,s(br)), 3.78 (2H,m), 4.57 (1H,d(br)), 5.02 (2H,s), 6.90 (2H,d), 7.13 (2H,d), 7.15-60 (8H,m).

10

Step 3:

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-[4-(benzyloxy)benzyl]-3-[[[(2,2-difluoro-1,3-benzodioxol-5-yl)sulfonyl](isobutyl)amino]-2-hydroxypropylcarbamate (340)

15



The carbamate formation was carried out as described for (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-benzyloxy-benzyl)-3-i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl)-carbamate. (Y=48%)

20

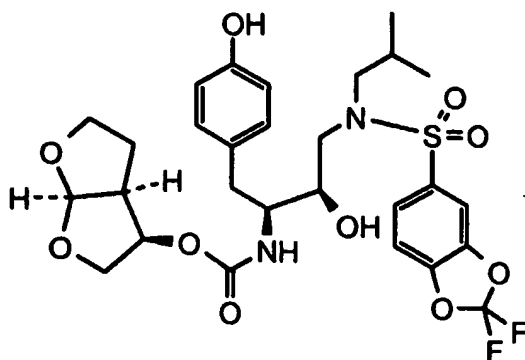
¹H-NMR (DMSO-d₆): δ 0.77 (3H,d), 0.82 (3H,d), 1.20 (1H,m),
 1.35 (1H,m), 1.90 (1H,m), 2.35 (1H,t), 2.70-3.00 (5H,m),
 3.04 (1H,dd), 3.40-3.60 (4H,m), 3.66 (1H,t), 3.80
 (1H,dd), 4.81 (1H,dd), 4.98 (1H,d), 4.99 (2H,s), 5.47
 5 (1H,d), 6.82 (2H,d), 7.06 (2H,d), 7.18 (1H,d), 7.20-7.45
 (5H,m), 7.56 (1H,d), 7.65 (1H,d), 7.81 (1H,s). MS: 719
 (M+1)⁺.

Example 124

10

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [[(2,2-difluoro-1,3-benzodioxol-5-
 yl)sulfonyl](isobutyl)amino]-2-hydroxy-1-(4-
 hydroxybenzyl)propylcarbamate (341)

15



20 The debenzylation was carried out as described for N-
 (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-oxycarbonyl-,
 (4S,5R)-4-(4-hydroxybenzyl)-5-i-butyl-[(3,4-
 methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-dimethyl-
 oxazolidine. (Y=100%)

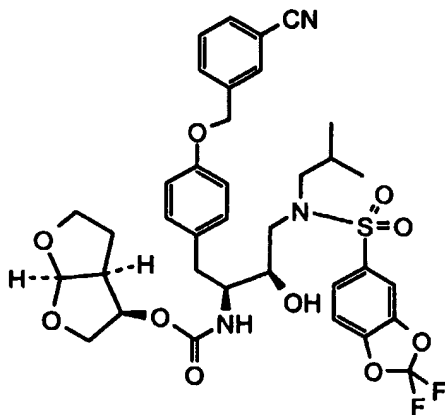
25

¹H-NMR (DMSO-d₆): δ 0.77 (3H,d), 0.82 (3H,d), 1.25 (1H,m),
 1.40 (1H,m), 1.92 (1H,m), 2.30 (1H,t), 2.70-3.00 (5H,m),
 3.02 (1H,dd), 3.40-3.60 (4H,m), 3.70 (1H,t), 3.80
 (1H,dd), 4.82 (1H,dd), 4.95 (1H,d), 5.47 (1H,d), 6.56
 5 (2H,d), 6.92 (2H,d), 7.13 (1H,d), 7.56 (1H,d), 7.64
 (1H,d), 7.81 (1H,s), 9.00 (1H,s).

10

Example 125

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-{4-
 [(3-cyanobenzyl)oxy]benzyl}-3-*i*[(2,2-difluoro-1,3-
 benzodioxol-5-yl)sulfonyl](isobutyl)amino]-2-
 15 hydroxypropylcarbamate (342)



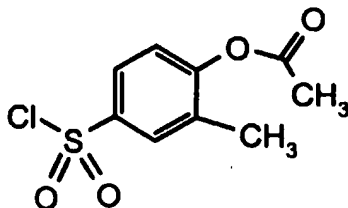
The alkylation step was carried out as described for N-
 20 (3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-yl-oxycarbonyl-,
 (4*S*,5*R*)-4-[4-(3-cyanobenzoyloxy)-benzyl]-5-*i*-butyl-[(3,4-
 methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-dimethyl-
 oxazolidine. (Y=84%)

¹H-NMR (DMSO-d₆): δ 0.77 (3H,d), 0.81 (3H,d), 1.21 (1H,m),
1.32 (1H,m), 1.92 (1H,m), 2.35 (1H,t), 2.65-3.00 (5H,m),
3.05 (1H,t), 3.40-3.60 (4H,m), 3.65 (1H,t(br)), 3.80
(1H,t(br)), 4.81 (1H,d(br)), 4.99 (1H,m), 5.08 (2H,s),
5 5.47 (1H,d), 6.84 (2H,d), 7.07 (2H,d), 7.19 (1H,d), 7.50-
7.90 (7H,m). MS: 744 (M+1)⁺.

Example 126

10 Step 1:

4-(chlorosulfonyl)-2-methylphenyl acetate



21 g (205 mmol) acetic anhydride was added to a stirred
15 mixture of 18.8 g (100 mmol) 3-methyl, 4-hydroxy sulfonic
acid in 100 ml dichloromethane. The mixture was stirred
for 12 hours, then the solvent was removed under reduced
pressure. The residue was dissolved in 100 ml ether, and
75 g (364 mmol) phosphorus pentachloride was added to the
20 stirred solution in small portions. After the addition,
the mixture was stirred for 15 minutes at 20 °C, then
poured into 500 g crushed ice. An additional 200 ml ether
was added, and the organic phase was separated, extracted
with cold water, then dried over anhydrous magnesium
25 sulfate. The solvent was removed under reduced pressure,
150 ml ether and 150 ml hexane was added, and the solid
was filtered. The filtrate was concentrated under reduced

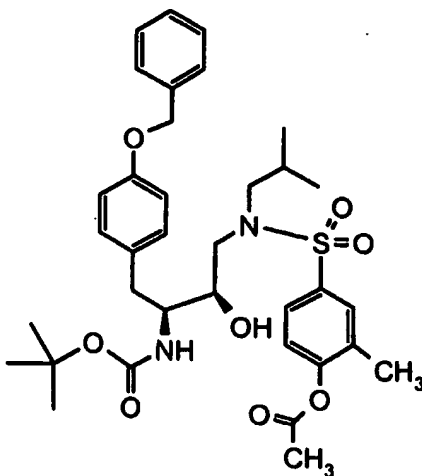
pressure again, then hexane (neat) was added, and the mixture was cooled to 0 °C. The solid was filtered, washed with cold hexane, and dried under reduced pressure, to yield 6.8 g (Y=27%) title compound.

5

¹H-NMR (CDCl₃): δ 2.29 (3H,s), 2.36 (3H,s), 7.27 (1H,d), 7.88 (1H,d), 7.91 (1H,s).

10 Step 2:

4-{[{(2*R*,3*S*)-4-[4-(benzyloxy)phenyl]-3-[(*tert*-butoxycarbonyl)amino]-2-hydroxybutyl}(isobutyl)amino]sulfonyl}-2-methylphenyl
15 acetate



The sulfonamide formation was carried out as described for *t*-Butyl-N[(1*S*,2*R*)-1-(4-benzyloxy-benzyl)-3-*i*-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl]-carbamate. (Y=74%)
20

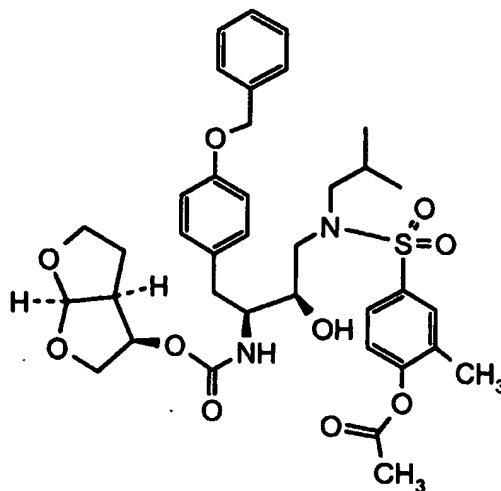
¹H-NMR (CDCl₃): δ 0.85 (3H,d), 0.89 (3H,d), 1.33 (9H,s), 1.84 (1H,m), 2.23 (3H,s), 2.32 (3H,s), 2.80-3.15 (6H,m),

3.86 (1H,s(br)), 3.77 (1H,s(br)), 3.90 (1H, s), 4.59 (1H,d), 5.02 (2H,s), 6.89 (2H,d), 7.10-7.25 (8H,m), 7.59 (1H,d), 7.64 (1H,s).

5 Step 3:

4-{[{(2R,3S)-3-({[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yloxy]carbonyl}amino)-4-[4-(benzyloxy)phenyl]-2-hydroxybutyl}(isobutyl amino)sulfonyl}-2-methylphenyl acetate (343)

10



The carbamate formation was carried out as described for (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-benzyloxy-benzyl)-3-i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl)-carbamate. (Y=29%)

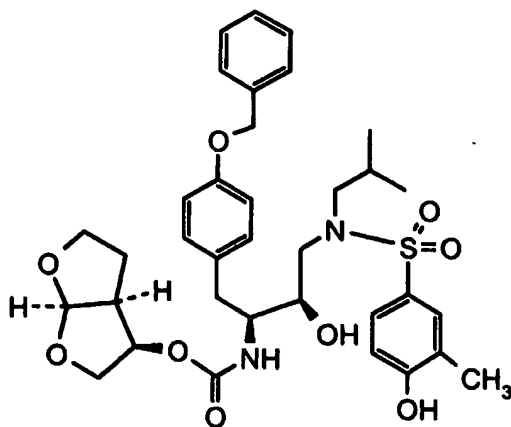
¹H-NMR (DMSO-d₆): δ 0.76 (3H,d), 0.81 (3H,d), 1.21 (2H,m), 1.32 (1H,m), 1.93 (1H,m), 2.16 (3H,s), 2.29 (3H,s), 2.36 (1H,t), 2.70-2.90 (3H,m), 2.93 (1H,d), 3.03 (1H,dd), 3.35 (1H,m), 3.45-3.60 (4H,m), 3.66 (1H, dd), 3.80 (1H,dd),

4.80 (1H,dd), 4.99 (3H,s), 5.46 (1H,d), 6.82 (2H,d), 7.07 (2H,d), 7.18 (1H,d), 7.22-7.42 (5H,m), 7.61 (1H,d), 7.70 (1H,s).

5

Example 127

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-[[4-(4-hydroxy-3-methylphenyl)sulfonyl](isobutyl)amino]propylcarbamate (344)



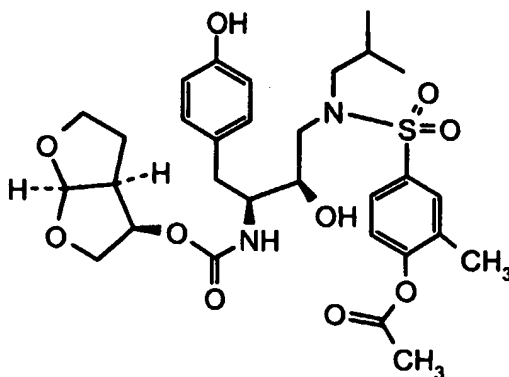
10

100 mg (0.14 mmol) product from the previous procedure dissolved in 10 ml methanol. 12 mg potassium carbonate was added to the solution, and the mixture was stirred for 30 minutes at 20 °C. The solvent was removed under reduced pressure, and the residue was dissolved in dioxane. The pH was adjusted to pH=4 with hydrochloric acid (4M in dioxane), the mixture was filtered, and the filtrate was concentrated under reduced pressure. The product crystallized from hexane-ethyl acetate (1:1) at 20 °C the yield 75 mg title compound. (Y=79%).

¹H-NMR (DMSO-d₆): δ 0.75 (3H,d), 0.81 (3H,d), 1.20 (1H,m), 1.30 (1H,m), 1.90 (1H,m), 2.12 (3H,s), 2.35 (1H,t), 2.60-2.80 (3H,m), 2.85-3.00 (2H,m), 3.40-3.60 (4H,m), 3.66 (1H,dd), 3.81 (1H,dd), 4.80 (1H,dd), 4.94 (1H,d), 5.00 (2H,s), 5.47 (1H,d), 6.85 (3H,m), 7.06 (2H,d), 7.18 (1H,d), 7.30-7.50 (6H,m), 10.3 (1H,s). MS: 669 (M+1)⁺.

Example 128

4-{[[(2R,3S)-3-({[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yloxy]carbonyl}amino)-2-hydroxy-4-(4-hydroxyphenyl)butyl](isobutyl)amino]sulfonyl}-2-methylphenyl acetate (345)



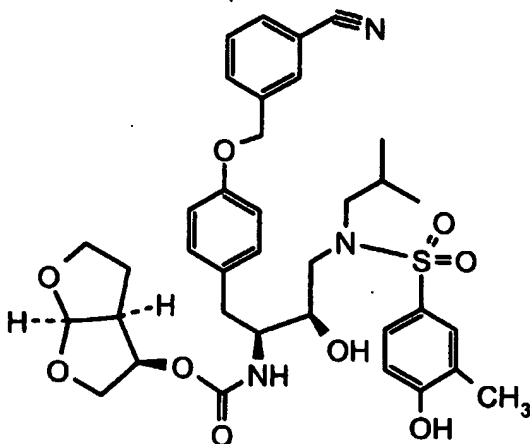
The debenzoylation was carried out as described for N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-oxycarbonyl-, (4S,5R)-4-(4-hydroxybenzyl)-5-i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-dimethyloxazolidine. (Y=quant.)

¹H-NMR (CDCl₃): δ 0.85 (3H,d), 0.88 (3H,d), 1.45 (1H,m), 1.62 (1H,m), 2.21 (3H,s), 2.32 (3H,s), 2.65 (1H,dd), 2.80- 3.15 (6H,m), 3.60-3.70 (3H, m), 3.75-3.95 (3H,m),

5.00 (1H,m), 5.21 (1H,d), 5.60 (1H,d), 6.65 (2H,d), 6.90-7.00 (3H,m), 7.15 (1H,d), 7.56 (1H,d), 7.62 (1H,s).

Example 129

5 (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-{4-[(3-cyanobenzyl)oxy]benzyl}-2-hydroxy-3-[[4-(4-hydroxy-3-methylphenyl)sulfonyl](isobutyl)amino]propylcarbamate (346)



10

The alkylation step was carried out as described for N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-oxycarbonyl-, (4S,5R)-4-[4-(3-cyanobenzyloxy)-benzyl]-5-i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-dimethyl-oxazolidine. The deacetylation step was carried out as described previously for (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-[[4-(4-hydroxy-3-methylphenyl)sulfonyl](isobutyl)amino]propylcarbamate.

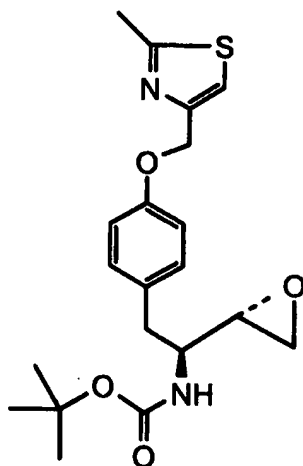
20 The final product was isolated by preparative HPLC. (Column: Luna C18, Solvent: 75% to 100 % MeOH/0.1%formic acid, t_{ret} : 4.08 min.) (Y=6 %, 2 steps, overall.)

MS: 694 (M+1)

Example 130

Step 1:

- 5 **tert-butyl (1*S*)-2-{4-[(2-methyl-1,3-thiazol-4-yl) methoxy]phenyl}-1-[(2*S*)-oxiranyl]ethylcarbamate**

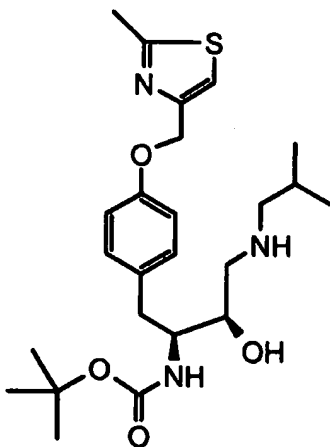


- 10 0.6 g (3.26 mmol) 4-Chloromethyl-2-methyl-thiazole hydrochloride was added to a stirred solution of 0.76 g (2.71 mmol) **tert-butyl (1*S*)-2-(4-hydroxyphenyl)-1-[(2*S*)-oxiranyl]ethylcarbamate** in 15 ml *N,N*-dimethylformamide. 3.25 g (10 mmol) cesium carbonate and 550 mg (3.66 mmol)
- 15 sodium iodide was added, and the mixture was stirred at 20 °C for 24 hours. 200 ml ethyl acetate was added, and the mixture was filtered. The filtrate was extracted with water (5x50 ml), and the organic phase was dried with anhydrous magnesium sulfate, filtered and concentrated
- 20 under reduced pressure. The residue was purified on silicagel column using hexane-ethyl acetate (1:1) as solvent to yield 820 mg (Y=78 %) title compound.

¹H-NMR (CDCl₃): δ 1.36 (9H,s), 2.71 (3H,s), 2.75-2.95 (4H,m), 3.61 (1H,s(br)), 4.39 (1H,s(br)), 5.11 (2H,s), 6.91 (2H,d), 7.11 (2H,d), 7.12 (1H,s).

5 Step 2:

tert-butyl (1S,2R)-2-hydroxy-3-(isobutylamino)-1-{4-[(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl}propylcarbamate



10 The ring-opening step was carried out as described previously for t-Butyl-(1S,2R)-1-(4-benzyloxy-benzyl)-3-i-butylamino-2-hydroxypropyl-carmamate. (Y=90%)

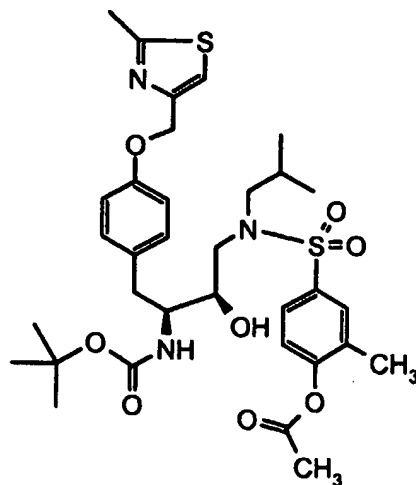
¹H-NMR (CDCl₃): δ 0.94 (6H,d), 1.39 (9H,s), 1.74 (1H,m),
 15 2.43 (2H,d), 2.70 (2H,m), 2.76 (3H,s), 2.80-3.00 (2H,m),
 3.46 (1H,m), 3.79 (1H,m), 4.68 (1H,d), 5.16 (2H,s), 6.94 (2H,d), 7.17 (1H,s), 7.18 (2H,d).

Step 3:

20

4-[[[(2R,3S)-3-[(tert-butoxycarbonyl)amino]-2-hydroxy-4-{4-[(2-methyl-1,3-thiazol-4-

yl)methoxy]phenyl}butyl) (isobutyl) amino] sulfonyl}-2-methylphenyl acetate



5

The sulfonamide formation was carried out as described for t-Butyl-N((1S,2R)-1-(4-benzyloxy-benzyl)-3-i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl)-carmamate. (Y=65%)

10

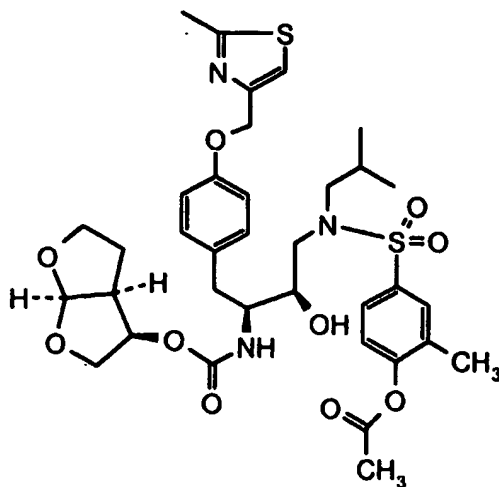
¹H-NMR (CDCl₃): δ 0.85 (3H,d), 0.87 (3H,d), 1.33 (9H,s), 1.82 (1H,m), 2.23 (3H,s), 2.32 (3H,s), 2.71 (3H, s), 2.80-3.00 (4H,m), 3.10 (2H,m), 3.68 (1H,s(br)), 3.77 (1H,s(br)), 3.91 (1H,s), 4.57 (1H,d), 5.10 (2H,s), 6.90 (2H,d), 7.12 (1H,s), 7.13 (2H,d), 7.59 (1H,d), 7.64 (1H,s).

15

Step 4:

20 4-{[[(2R,3S)-3-({[(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yloxy]carbonyl)amino]-2-hydroxy-4-{4-[(2-methyl-1,3-

thiazol-4-yl)methoxy]phenyl}butyl) (isobutyl) amino]
sulfonyl}-2-methylphenyl acetate (347)



5 The carbamate formation was carried out as described for
(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-
(4-benzyloxy-benzyl)-3-i-butyl-[(3,4-
methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl-
carmamate. (Y=44%)

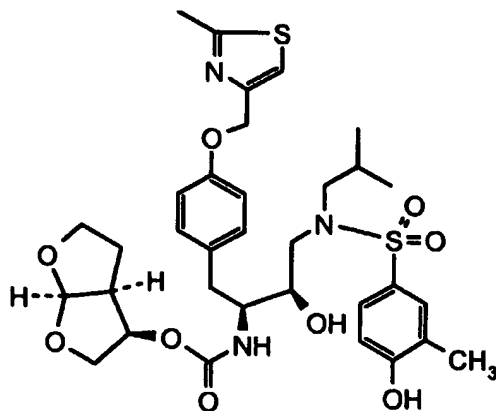
10

¹H-NMR (DMSO-d₆): δ 0.76 (3H,d), 0.81 (3H,d), 1.34 (1H,m),
1.94 (1H,m), 2.16 (3H,s), 2.30 (3H,s), 2.36 (1H,t), 2.61
(3H,s), 2.70-3.10 (5H,m), 3.45-3.60 (3,m), 3.68 (1H,t),
3.79 (1H,t), 4.81 (1H,m), 4.99 (3H, sm), 5.46 (1H,d),
15 6.84 (2H,d), 7.08 (2H,d), 7.20 (1H,d), 7.26 (1H,d), 7.48
(1H,d), 7.61 (1H,d), 7.70 (1H,s). MS: 732 (M+1)⁺.

Example 131

20 (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-2-
hydroxy-3-[[4-(4-hydroxy-3-methylphenyl)sulfonyl] (isobutyl)

amino]-1-[4-[(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl]
propylcarbamate (348)



5

Procedure:

The deacetylation step was carried out as described previously for (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-1-[4-(benzyloxy)benzyl]-2-hydroxy-3-[[4-
10 hydroxy-3-methylphenyl)sulfonyl](isobutyl)amino] propylcarbamate. (Y=94%)

¹H-NMR (DMSO-*d*₆): δ 0.75 (3H,s(br)), 0.81 (3H,s(br)), 1.20 (1H,m), 1.32 (1H,m), 1.91 (1H,m), 2.12 (3H,s), 2.36
15 (1H,t), 2.61 (3H,s), 2.65-3.00 (5H,m), 3.40-3.60 (4H,m), 3.68 (1H,s(br)), 3.81 (1H,s(br)), 4.80 (1H,m), 4.99 (3H,s+m), 5.40 (1H,s(br)), 6.85 (4H,m), 7.07 (2H,m), 7.17 (1H,d), 7.35-7.50 (3H,m), 10.30 (1H,s). MS: 690 (M+1)⁺.

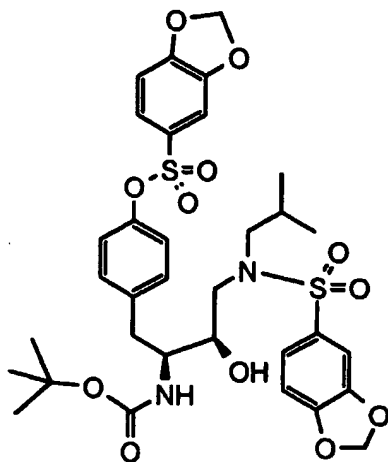
20

Example 132

Step 1:

4-{(2*S*,3*R*)-4-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-[(tert-

butoxycarbonyl) amino] -3-hydroxybutyl}phenyl 1,3-benzodioxole-5-sulfonate



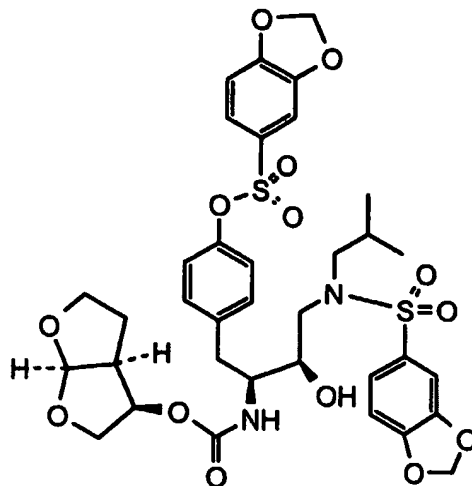
5

The reaction was carried as described for the synthesis of 4-((2*S*,3*R*)-2-(((tert-butoxycarbonyl)amino]-3-hydroxy-4-
 10 {isobutyl[(4-nitrophenyl)sulfonyl]amino}butyl)phenyl 4-nitrobenzenesulfonate.

¹H-NMR (CDCl₃): δ 0.86 (3H,d), 0.89 (3H,d), 1.33 (9H,s),
 1.81 (1H,m), 2.75-3.10 (6H,m), 3.68 (1H,s(br)), 3.76
 15 (1H,s(br)), 3.95 (1H,s), 4.60 (1H,d), 6.07 (2H,s), 6.09
 (2H,s), 6.80-6.95 (4H, m), 7.10-7.35 (6H,m).

Step 2:

20 4-{{(2*S*,3*R*)-2-({[(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yloxy]carbonyl}amino)-4-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-3-hydroxybutyl}phenyl 1,3-benzodioxole-5-sulfonate (349)



5

The reaction was carried as described for the synthesis of 4-((2*S*,3*R*)-2-(((3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-

10 b)furan-3-yloxy]carbonyl)amino)-3-hydroxy-4-{isobutyl[(4-nitrophenyl)sulfonyl]amino}butyl)phenyl 4-

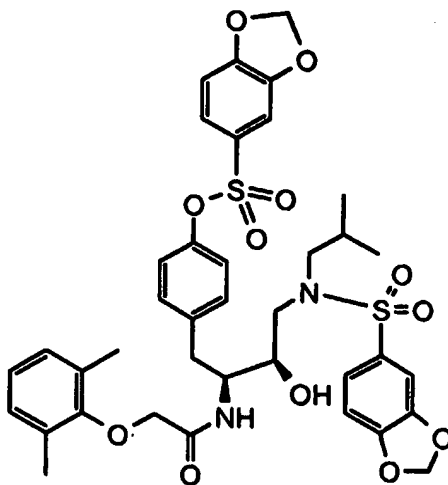
¹H-NMR (DMSO-d₆): δ 0.75 (3H,d), 0.81 (3H,d), 1.20 (1H,m), 1.35 (1H,m), 1.91 (1H,m), 2.41 (1H,t), 2.60-2.80 (3H,m), 2.98 (2H,m), 3.20-3.40 (2H,m), 3.40-3.60 (4H,m), 3.66

15 (1H,t), 3.80 (1H,t), 4.80 (1H,dd), 5.04 (1H, s), 5.47 (1H,d), 6.13 (2H,s), 6.19 (2H,s), 6.90 (2H,d), 7.04 (2H,m), 7.10-7.40 (6H,m). MS: 777 (M+1)⁺.

20

Example 133

4-((2*S*,3*R*)-4-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-[[2,6-dimethylphenoxy)acetyl]amino]-3-hydroxybutyl)phenyl 1,3-benzodioxole-5-sulfonate (350)



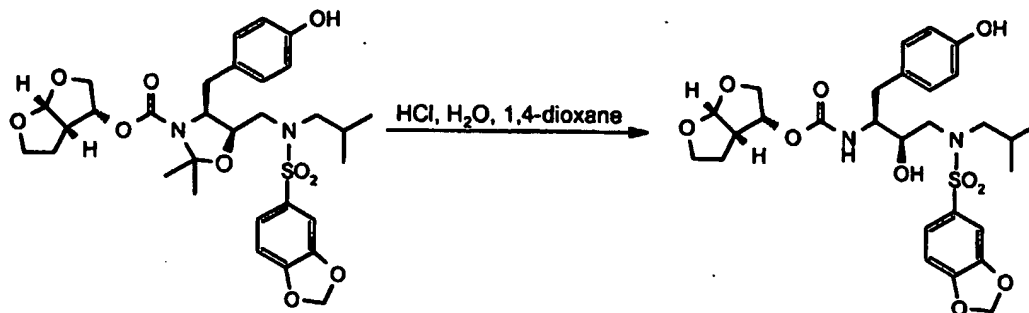
5

The coupling reaction was carried as described for the synthesis of *N*-{(1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-(benzyloxy)benzyl]-2-hydroxypropyl}-2-(2,6-dimethylphenoxy)acetamide.

¹H-NMR (DMSO-*d*₆): δ 0.77 (3H,d), 0.81 (3H,d), 1.94 (1H,m), 2.07 (6H,s), 2.60-2.90 (3H,m), 2.90-3.10 (2H,m), 3.68 (1H,m), 3.81 (1H,d), 3.96 (1H,m), 4.05 (1H,d), 5.10 (1H,d), 6.12 (4H,m), 6.85-7.05 (7H,m), 7.15-7.35 (6H,m), 7.93 (1H,d). MS: 783 (M+1)⁺

15

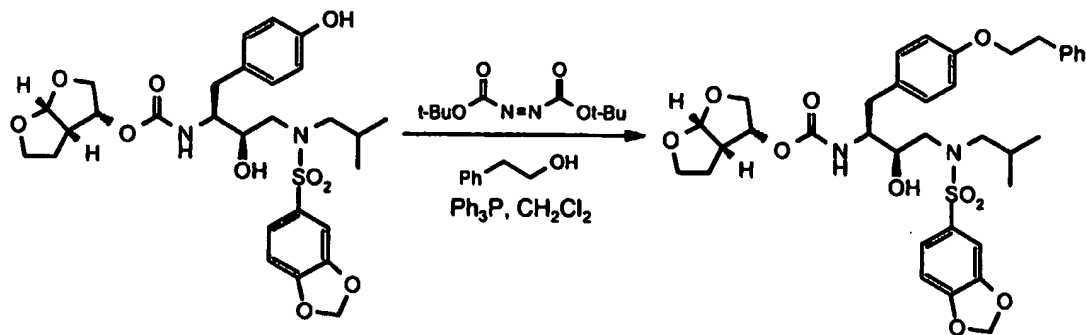
Example 134



(3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl) (isobutyl) amino]-2-
 5 hydroxy-1-(4-hydroxybenzyl)propylcarbamate (351)

A solution of 0.60 g (0.95 mmol) of
 (3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl (4*S*, 5*R*)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl) (isobutyl) amino] methyl}-
 4-(4-hydroxybenzyl)-2,2-dimethyl-1,3-oxazolidine-3-
 10 carboxylate in 5 mL of 1,4-dioxane was treated with 0.25
 mL of water followed by 5 mL of 4*N* HCl in 1,4-dioxane and
 the resulting solution was stirred at RT. After 1.5
 hours the solution was diluted with 25 mL of CH₂Cl₂ and
 the pH adjusted to approximately 12 by addition of 1*N*
 15 aqueous NaOH. The mixture was diluted with water and
 extracted with CH₂Cl₂ (3x). The combined CH₂Cl₂ extracts
 were washed with aqueous brine (3x), dried over MgSO₄, and
 concentrated in vacuo. The residue was subjected to
 flash chromatography (SiO₂, 8:2 EtOAc/hexane) to afford
 20 the desired compound as a white solid in 81% yield. ¹H NMR
 (CDCl₃): 7.29 (dd, 1H), 7.13 (s, 1H), 7.01 (d, 2H), 6.85
 (d, 2H), 6.70 (d, 2H), 6.05 (s, 2H), 5.61 (d, 1H), 5.01
 (m, 2H), 3.92 (dd, 1H), 3.80 (m, 4H), 3.68 (m, 2H), 3.08
 (dd, 1H), 2.91 (m, 5H), 2.81-2.62 (m, 2H), 1.80 (m, 1H),
 25 1.64 (m, 1H), 1.47 (m, 1H), 0.90 (d, 3H), 0.82 (d, 3H).
 MS(ESI): 593 (M+H).

Example 135



(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-

5 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-[4-(phenethoxy)benzyl]propylcarbamate (352)

To a solution of 66 mg (0.25 mmol) of triphenylphosphine and 30 μ L (0.25 mmol) of phenethyl alcohol in 3 mL of anhydrous CH_2Cl_2 was added 58 mg (0.25 mmol) of di-tert-butyl azodicarboxylate. The resulting solution was

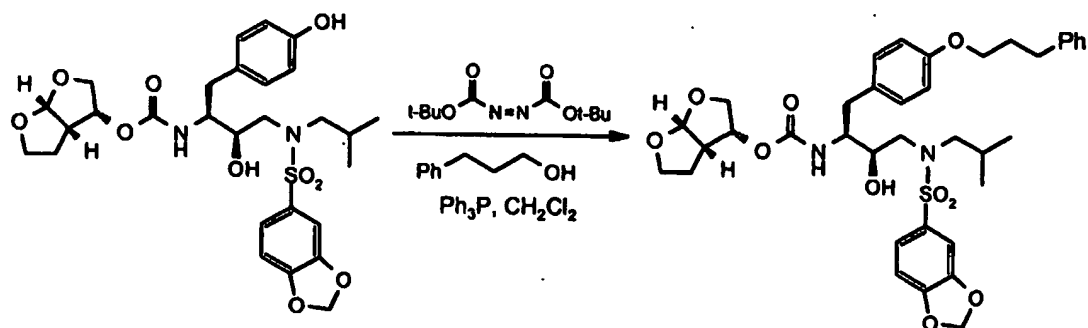
10 stirred at RT for 5 minutes and was then treated with a solution of 50 mg (0.084 mmol) of

(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-

15 hydroxy-1-(4-hydroxybenzyl)propylcarbamate in 2 mL of CH_2Cl_2 . After stirring at RT for 1.5 hours the solution was concentrated to dryness and the residue purified by flash chromatography (SiO_2 , 4:6 hexane/EtOAc) to give the desired product as a white foam in 72% yield. ^1H NMR

20 (CDCl_3): 7.34-7.17 (m, 6H), 7.15 (s, 1H), 7.07 (d, 2H), 6.86 (d, 1H), 6.78 (d, 2H), 6.03 (s, 2H), 5.61 (d, 1H), 4.98 (m, 1H), 4.86 (d, 1H), 4.09 (t, 2H), 3.92 (m, 1H), 3.84-3.56 (m, 6H), 3.17-3.01 (m, 3H), 3.00-2.81 (m, 4H), 2.80-2.64 (m, 2H), 1.78 (m, 1H), 1.56 (m, 1H), 1.47 (m,

25 1H), 0.91 (d, 3H), 0.85 (d, 3H). MS(ESI): 697(M+H).

Example 136

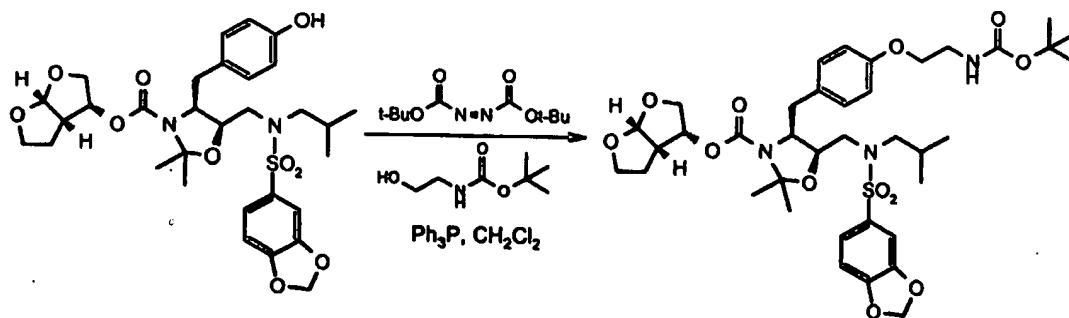
5 (3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy
 -1-[4-([3-phenylpropyl]oxy)benzyl]propylcarbamate (353)

The title compound was prepared according to example 135
 with the exception that 3-phenyl-1-propanol was used

10 instead of phenethyl alcohol. ¹H NMR (CDCl₃): 7.33-7.11
 (m, 7H), 7.07 (d, 2H), 6.86 (d, 1H), 6.76 (d, 2H), 6.04
 (s, 2H), 5.61 (d, 1H), 4.99 (q, 1H), 4.86 (d, 1H), 3.97-
 3.72 (m, 7H), 3.65 (m, 2H), 3.09 (dd, 1H), 3.01-2.81 (m,
 4H), 2.80-2.64 (m, 4H), 2.06 (m, 2H), 1.85-1.40 (m, 3H),
 15 0.91 (d, 3H), 0.84 (d, 3H). MS(ESI): 711(M+H).

Example 137

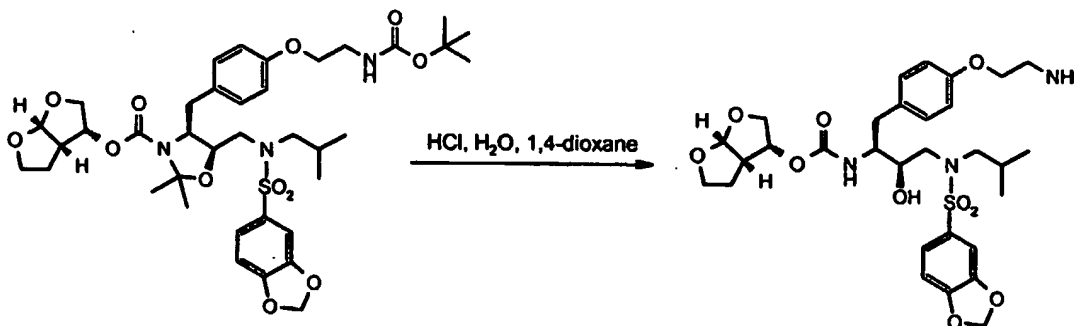
Step 1:



(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (4S,5R)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 4-(4-[2-(tert-butoxycarbonylamino)ethoxy]benzyl)-2,2-
 dimethyl-1,3-oxazolidine-3-carboxylate

- 5 According to example 135 (with the exception that N-
 (tert-butoxycarbonyl)ethanolamine was used instead of
 phenethyl alcohol), (3R,3aS,6aR)hexahydrofuro[2,3-
 b]furan-3-yl (4S,5R)-5-{[(1,3-benzodioxol-5-
 ylsulfonyl)(isobutyl)amino]methyl}-4-(4-hydroxybenzyl)-
 10 2,2-dimethyl-1,3-oxazolidine-3-carboxylate was converted
 to the desired compound. MS(ESI): 798 (M+Na).

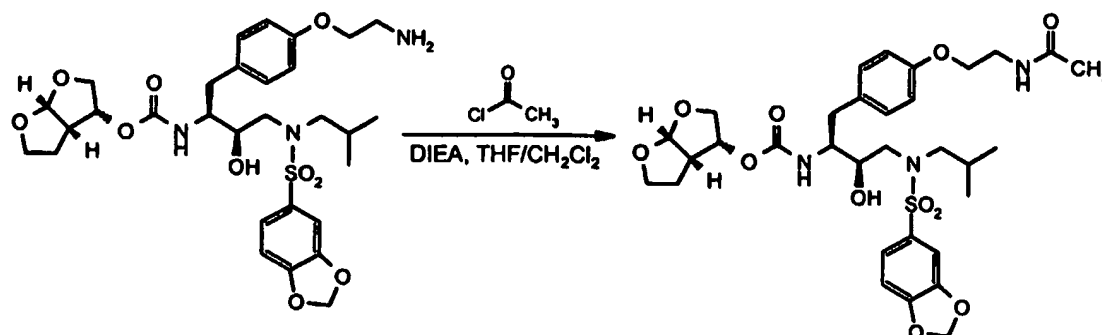
Step 2:



15

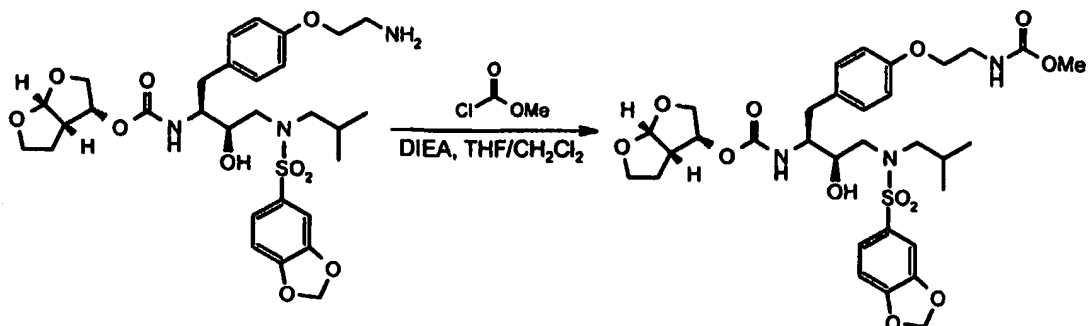
(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(2-aminoethoxy)benzyl]propylcarbamate (354)

- 20 The title compound was prepared according to example 134.
¹H NMR (CDCl₃): 7.39 (dd, 1H), 7.12 (s, 1H), 7.08 (d, 2H),
 6.84 (d, 1H), 6.77 (d, 2H), 6.03 (s, 2H), 5.61 (d, 1H),
 4.95 (m, 2H), 4.00-3.60 (m, 8H), 3.16-2.62 (m, 10H),
 2.20-1.40 (m, 5H), 0.90 (d, 3H), 0.82 (d, 3H). MS(ESI):
 25 636 (M+H).

Example 138

5 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(2-[acetylamino]ethoxy)benzyl]
 propylcarbamate (355)

A solution of 21 mg (0.033 mmol) of
 10 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(2-aminoethoxy)benzyl]propylcarbamate in 2
 mL of 1:1 THF/CH₂Cl₂ was treated with 9 µL (0.050 mmol) of
 N,N-diisopropylethylamine followed by 2.6 µL (0.036 mmol)
 15 of acetyl chloride. The resulting solution was stirred
 at RT. After 1.5 hours the solution was concentrated in
 vacuo and the residue subjected to flash chromatography
 (SiO₂, 95:5 CH₂Cl₂/MeOH) to afford the desired compound in
 86 % yield as a white foam. ¹H NMR (CDCl₃): 7.29 (dd, 1H),
 20 7.16-7.04 (m, 3H), 7.05 (d, 1H), 6.76 (d, 2H), 6.05 (s,
 2H), 5.91 (br s, 1H), 5.01 (d, 1H), 5.05-4.89 (m, 2H),
 3.94 (m, 3H), 3.80 (m, 3H), 3.72-3.51 (m, 5H), 3.08 (dd,
 1H), 3.01-2.83 (m, 4H), 2.74 (m, 2H), 1.97 (s, 3H), 1.86-
 1.45 (m, 3H), 0.90 (d, 3H), 0.84 (d, 3H). MS(ESI):
 25 678 (M+H).

Example 139

5

(3*R*,3*aS*,6*aR*)hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(2-[(methoxycarbonyl)amino]ethoxy)

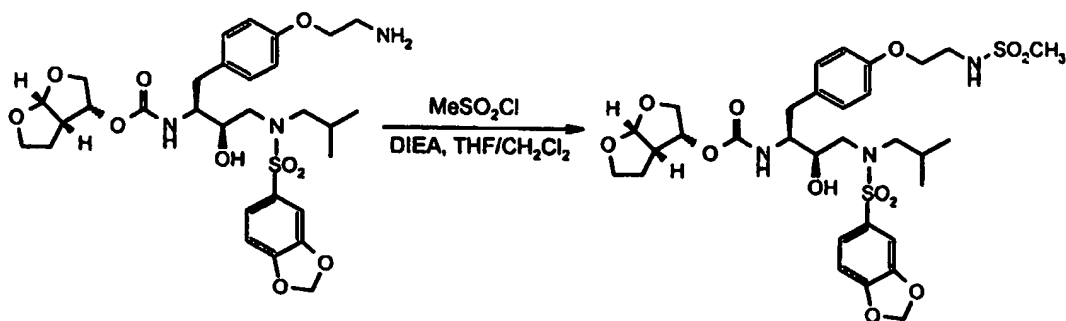
10 **benzyl]propylcarbamate (356)**

The title compound was prepared according to example 138
 with the exception that methyl chloroformate was used
 instead of acetyl chloride. ¹H NMR (CDCl₃): 7.29 (dd, 1H),
 7.16-7.02 (m, 3H), 6.84 (d, 1H), 6.76 (d, 2H), 6.04 (s,
 2H), 5.61 (d, 1H), 5.18-4.84 (m, 3H), 4.02-3.43 (m, 14H),
 3.09 (m, 1H), 2.91 (m, 4H), 2.72 (m, 2H), 1.85-1.43 (m,
 3H), 0.89 (d, 3H), 0.92 (d, 3H). MS(ESI): 694 (M+H).

15

Example 140

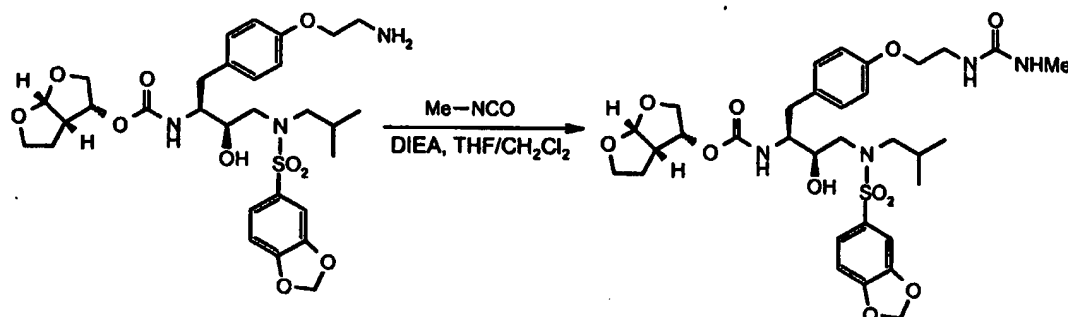
20



(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(2-[(methylsulfonyl)amino]ethoxy)
 benzyl]propylcarbamate (357)

- 5 The title compound was prepared according to example 138
 with the exception that methanesulfonyl chloride was used
 instead of acetyl chloride. ¹H NMR (CDCl₃): 7.29 (dd, 1H),
 7.11 (m, 3H), 6.86 (d, 1H), 6.77 (d, 2H), 6.04 (s, 2H),
 5.61 (d, 1H), 4.98 (m, 2H), 4.84 (m, 1H), 4.09-3.44 (m,
 10 11H), 3.12-2.82 (m, 8H), 2.74 (m, 2H), 1.88-1.43 (m, 3H),
 0.89 (d, 3H), 0.81 (d, 3H). MS(ESI): 714(M+H).

Example 141

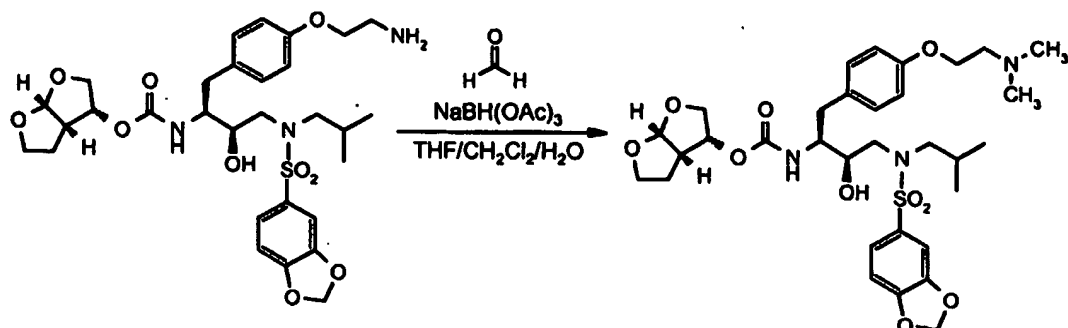


15

(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(2-[(methylamino]carbonyl)amino]
 20 ethoxy)benzyl]propylcarbamate (358)

The title compound was prepared according to example 138
 with the exception that methyl isocyanate was used
 instead of acetyl chloride.

- ¹H NMR (CDCl₃): 7.29 (dd, 1H), 7.13 (s, 1H), 7.08 (d, 2H),
 25 6.84 (d, 1H), 6.76 (d, 2H), 6.05 (s, 2H), 5.61 (d, 1H),
 5.10-4.90 (m, 2H), 4.04-3.48 (m, 11H), 3.15-2.67 (m,
 10H), 1.80 (m, 1H), 1.62 (m, 1H), 1.47 (m, 1H), 0.85 (m,
 6H). MS(ESI): 693(M+H).

Example 142

5

(3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(2-[dimethylamino]ethoxy)benzyl]

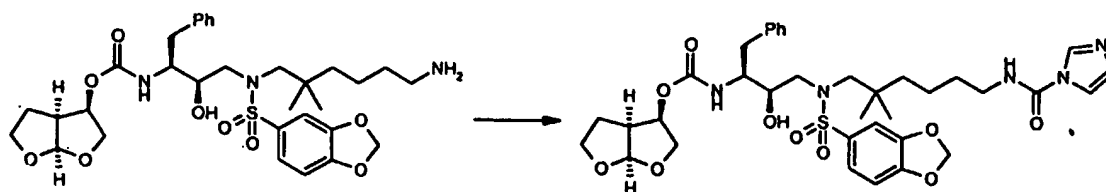
10 **propylcarbamate (359)**

A solution of 21 mg (0.033 mmol) of
 (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-(2-aminoethoxy)benzyl]propylcarbamate in 3
 15 mL of 8:2 THF/CH₂Cl₂ was treated with 13 µL (0.17 mmol) of
 37% aqueous formaldehyde followed by 35 mg (0.17 mmol) of
 NaBH(OAc)₃ and the resulting cloudy solution was stirred
 at RT. After 3 hours the solution was filtered to remove
 solids and the filtrate concentrated *in vacuo*. The
 20 residue was purified by flash chromatography (SiO₂, 95:5
 CH₂Cl₂/2M NH₃ in MeOH) to give the desired compound as a
 white foam in 68% yield. ¹H NMR (CDCl₃): 7.29 (dd, 1H),
 7.13 (s, 1H), 7.07 (d, 2H), 6.85 (d, 1H), 6.80 (d, 2H),
 6.03 (s, 2H), 5.61 (d, 1H), 4.98 (q, 1H), 4.89 (d, 1H),
 4.01 (t, 2H), 3.92 (m, 1H), 3.80 (m, 3H), 3.66 (m, 2H),
 25 3.09 (dd, 1H), 2.92 (m, 5H), 2.74 (m, 4H), 2.32 (s, 6H),

1.80 (m, 1H), 1.63 (m, 1H), 1.42 (m, 1H), 0.90 (d, 3H),
0.84 (d, 3H). MS(ESI): 664 (M+H).

Example 143

- 5 (3R,3aS,6aR)-Hexahydro[2,3-b]furan-3-yl N-((1S,2R)-1-benzyl-3-[6-(N'-carbonylimidazol-1-yl)amino-2,2-dimethylhexyl][(3,4-methylenedioxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (360)



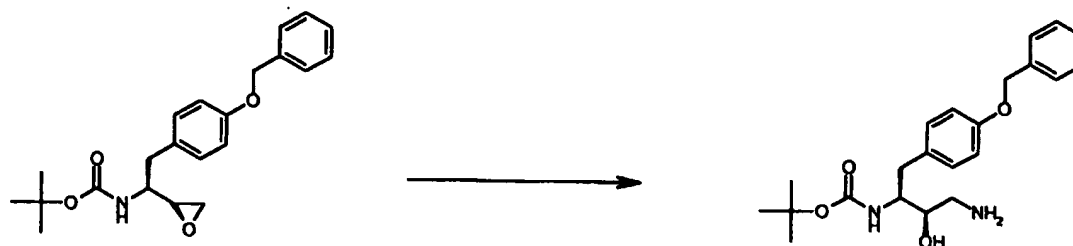
- 10 To a solution of (3R,3aS,6aR)-hexahydro[2,3-b]furan-3-yl N-((1S,2R)-1-benzyl-3-[6-amino-2,2-dimethylhexyl][(3,4-methylenedioxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (0.12 g, 0.19 mmol) in dichloromethane (1.5 mL) was added 1,1'-
- 15 carbonyldiimidazole (0.06 g, 0.37 mmol) and the mixture was stirred for 30 min at ambient temperature. The mixture was diluted with dichloromethane and washed with 5% citric acid/water (2X), saturated sodium bicarbonate/water, dried (sodium sulfate), evaporated,
- 20 and dried in vacuo to provide the title compound (0.14 g) as a solid foam; ¹H NMR (DMSO-d₆): 0.90 (6H, s), 1.12 (1H, dd), 1.20-1.35 (4H, m), 1.5 (2H, br s), 2.4 (1H, t), 2.7-2.8 (2H, m), 2.9-3.0 (2H, m), 3.2 (2H, dd), 3.25-3.35 (3H, m), 3.4 (1H, quartet), 3.5-3.6 (2H, m), 3.65 (1H, t), 3.75 (1H, quartet), 3.8 (1H, dd), 4.8 (1H, quartet),
- 25 5.1 (1H, d), 5.5 (1H, d), 6.15 (2H, s), 6.98 (1H, s),

7.0 (1H, d), 7.10-7.25 (7H, m), 7.3 (1H, d), 7.6 (1H, s), 8.2 (1H, s), 8.4 (1H, t); MS: 742 (MH⁺); C₃₆H₄₇N₅O₁₀S.

Example 144

5 Step 1:

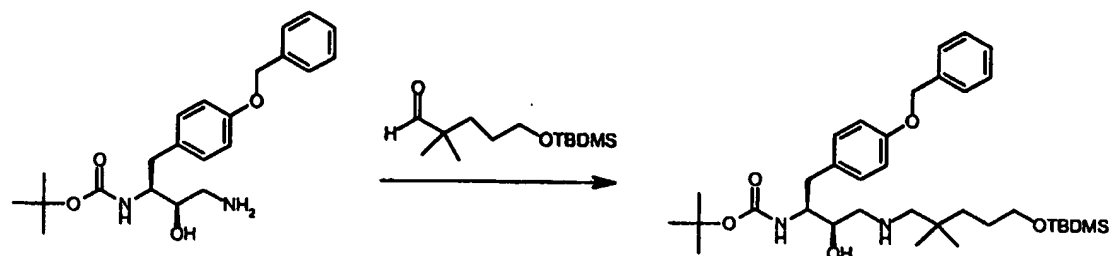
tert-Butyl N-(1*S*,2*R*)-1-benzyl-3-amino-1-[(4-benzyloxy)benzyl]-2-hydroxypropylcarbamate



- 10 To a saturated solution of ammonia in methanol (100mL) at 5 °C was added the epoxide (1.0g, 2.8mmol). Ammonia gas was continuously bubbled through the solution for an additional hour. The reaction was allowed to come to ambient temperature and stir for 48 hours. The methanol
- 15 was removed in vacuo and the resulting solid was triturated with ether (50mL), filtered and dried to afford the title compound (910mg, 85%) as a white solid.
- 1H NMR (DMSO-d₆): 1.22 (9H, s), 1.58 (2H, br), 2.41-2.53 (3H, m), 2.89 (1H, dd), 3.15-3.19 (1H, m), 3.33-3.45 (1H, m), 4.70 (1H, br), 5.00 (2H, s), 6.58 (1H, d), 6.83 (2H, d), 7.04 (2H, d), 7.25-7.39 (5H, m)
- 20

Step 2:

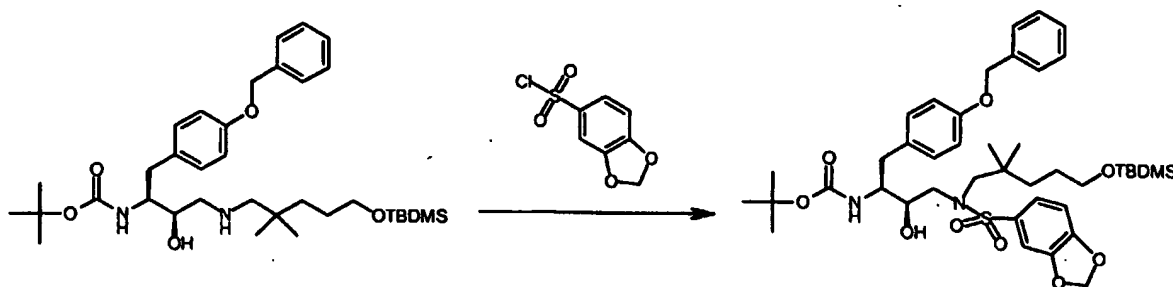
**tert-Butyl N-(1S,2R)-1-[(4-benzyloxy)benzyl]-3-[(5-tert-butyl-
butyldimethylsilyloxy-2,2-dimethyl)amino]-2-
hydroxypropylcarbamate**



- 5 To a stirred suspension of the above amine) (5.04g, 13.0mmol) in N,N-dimethylformamide (35mL), 1,2-dichloroethane (35mL) and glacial acetic acid (.5mL) was added a solution of 5-tert-butyldimethylsilyloxy-2,2-dimethylpentanal (2.66g, 10.9mmol) in tetrahydrofuran
- 10 (35mL) over 15 minutes. Sodium triacetoxyborohydride (2.76g, 13.0mmol) was added and the mixture was stirred under nitrogen for 18 hours. The reaction was concentrated in vacuo to approximately 1/3 volume, added cold 2.5% sodium hydroxide (100mL) and extracted with
- 15 ethyl acetate (2x100mL). The combined ethyl acetate was washed with water (2x50mL), dried (magnesium sulfate) and concentrated. The residue was triturated with ether and the resulting solid (amine starting material) was filtered away. The filtrate was concentrated in vacuo to
- 20 afford the desired crude product (6.80g, 6.54 theory) as a thick paste. The material was used without further purification.

Step 3:

**tert-Butyl N-((1S,2R)-1-[(4-benzyloxy)benzyl]-3-(5-tert-butyl-
 butyldimethylsilyloxy-2,2-dimethylpentyl)[(3,4-
 methylenedioxyphenyl)sulfonyl]amino-2-
 hydroxypropyl)carbamate**

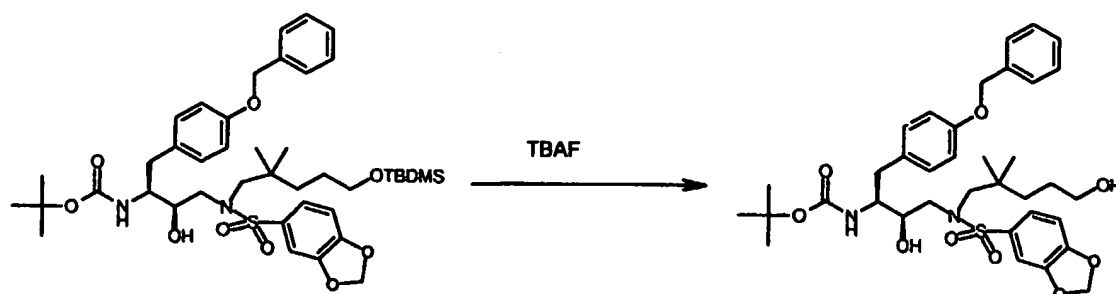


5

To a stirred solution of the crude amine from step 2, (6.80g), and N,N-diisopropylethylamine (3.7mL, 21.8mmol) in anhydrous dichloromethane (70mL) at 5 °C was added a solution of 3,4-methylenedioxyphenylsulfonyl chloride
 10 (2.88g, 13.0mmol) in dichloromethane (30mL) over 15 minutes. The mixture was allowed to warm to ambient temperature and stir for 16 hours. The reaction was concentrated in vacuo, taken up in ethyl acetate (100mL), washed with water (50mL), 1N hydrochloric acid (2x50mL),
 15 water (50mL), saturated sodium bicarbonate (2x50mL), dried (magnesium sulfate) and concentrated in vacuo to afford the desired crude product (8.55g) as a white foam. The material was used without further purification.

Step 4:

20 **tert-Butyl N-((1S,2R)-1-[(4-benzyloxy)benzyl]-3-(2,2-dimethyl-5-hydroxypentyl)[(3,4-methylenedioxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate**

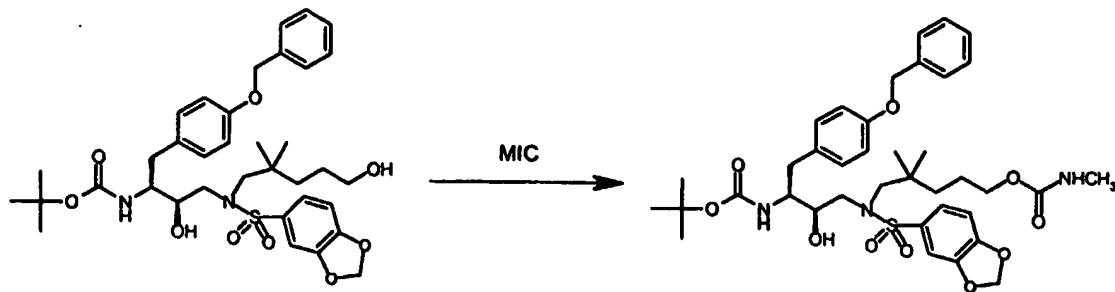


To a stirred solution of the crude product from step 3.) (8.5g, 10.6mmol) in tetrahydrofuran (85mL) was added tetrabutylammonium fluoride (13.8mL, 1M in tetrahydrofuran) over 15 minutes. After stirring for 18 hours, the reaction was concentrated *in vacuo*, added ether (100mL) and washed with water (3x50mL). The ether was dried (magnesium sulfate) and concentrated to a foam. Taken up in fresh ether (40mL) and stirred at ambient temperature for 120 hours. The resulting precipitate was filtered, rinsed with ether/hexane (1:1, 25mL) and dried to afford the title compound (3.2g, 44%) as a white solid. The filtrate was concentrated to a foam (2.95g). HPLC analysis showed approximately 65% product (not isolated). ¹H NMR (DMSO-d₆): 0.86 (6H, s), 1.11-1.23 (2H, m), 1.19 (9H, s), 1.30-1.35 (2H, m), 2.37 (1H, dd), 2.77-2.82 (2H, m), 2.91-2.97 (1H, m), 3.25-3.33 (5H, m), 3.61-3.67 (1H, m), 4.33 (1H, t), 4.89 (1H, d), 5.00 (2H, s), 6.11 (2H, s), 6.52 (1H, d), 6.82 (2H, d), 6.98-7.04 (3H, m), 7.22-7.38 (7H, m)

Step 5:

tert-Butyl N-((1S,2R)-1-[(4-benzyloxy)benzyl]-3-(2,2-dimethyl-5-N'-methylcarbamoyloxy)pentyl)[(3,4-

methylenedioxyphenyl) sulfonyl] amino-2-hydroxypropyl) carbamate

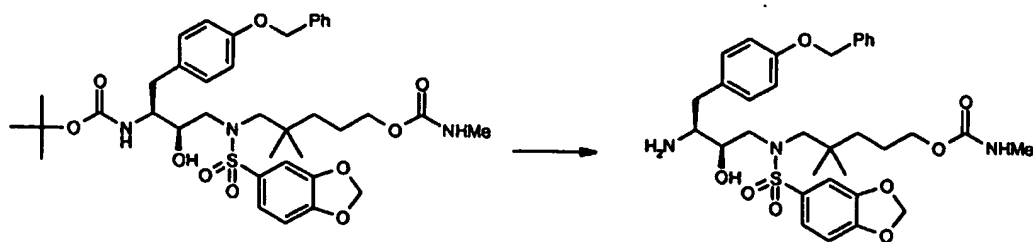


To a stirred solution of the alcohol from step 4.)
 5 (600mg, .88mmol) in dichloromethane (6mL) was added methylisocyanate (1.0mL, 17.50mmol). After stirring at ambient temperature for 48 hours, the reaction was concentrated in vacuo and purified by silica gel chromatography (1:1; ethyl acetate: hexane) to afford the
 10 title compound (570mg, 88%) as a white foam. ¹H NMR (DMSO-d₆): 0.86 (6H, d), 1.18-1.23 (2H, m), 1.19 (9H, s), 1.43-1.49 (2H, m), 2.37 (1H, dd), 2.50 (3H, d), 2.77-2.82 (2H, m), 2.90-2.96 (1H, m), 3.28-3.31 (3H, m), 3.61-3.67 (1H, m), 3.84 (2H, t), 4.91 (1H, d), 5.00 (2H, s), 6.11 (1H, d),
 15 6.52 (1H, d), 6.81-6.86 (3H, m), 6.98-7.04 (3H, m), 7.23-7.38 (7H, m)

Step 6:

N1-[(2R,3S)-3-amino-4-[(4-benzyloxy)phenyl]butyl]-N1-[2,2-dimethyl-5-(N2-methylcarbamoyloxy)pentyl]-3,4-methylenedioxy-1-benzenesulfonamide

20



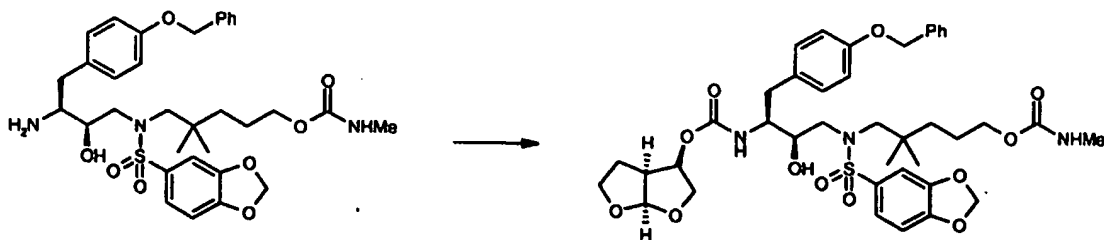
Treatment of the product from step 5 with trifluoroacetic acid/dichloromethane as previously described provided the title compound as a solid foam; ^1H NMR ($\text{DMSO}-d_6$): 0.8

5 (6H, d), 1.2-1.3 (2H, m), 1.4-1.5 (2H, m), 2.2 (1H, dd), 2.55 (3H, d), 2.6-2.7 (2H, m), 2.9 (1H, d), 3.1 (1H, dd), 3.2-3.3 (3H, m), 3.5 (2H, br d), 3.85 (2H, t), 4.6 (1H, d), 5.05 (2H, s), 6.1 (2H, s), 6.9 (3H, br d), 7.0 (1H, d), 7.08 (2H, br d), 7.2-7.4 (7H, m); MS: 642 (MH^+)

10

Step 7:

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl N-((1S,2R)-1-
 [(4-benzyloxy)benzyl-3-[2,2-dimethyl-5-(N'-
 methylcarbamoyloxy)-pentyl][(3,4-methylenedioxyphenyl)
 15 sulfonyl]amino-2-hydroxypropyl)carbamate (361)



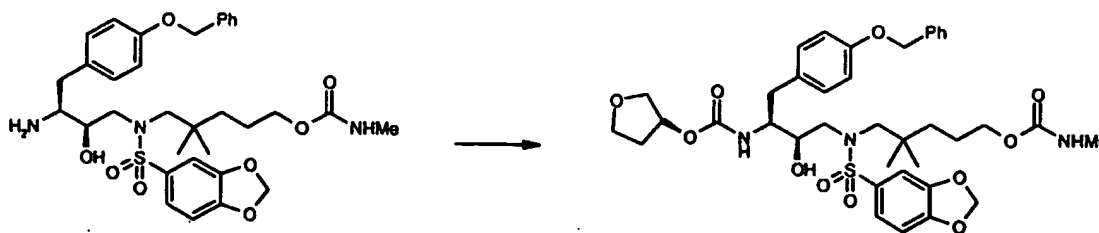
To a solution of the product from step 6 (0.11 g, 0.17 mmol) in acetonitrile (3 mL) was added

20 diisopropylethylamine (0.076 mL, 0.057 g, 0.44 mmol) and

[(3*R*, 3*aS*, 6*aR*) hexahydrofuro[2,3-*b*]furan-3-yl] [4-nitrophenyl] carbonate (0.065 g, 0.22 mmol) and the mixture was stirred at ambient temperature for 24 h. Solvent was evaporated and the residue was dissolved in ethyl acetate, washed with saturated sodium bicarbonate/water (4X), dried (sodium sulfate), concentrated, and chromatographed (silica gel; hexanes/ethyl acetate) to provide the title compound as a solid foam; ¹H NMR (DMSO-*d*₆): 0.9 (6H, d), 1.1-1.3 (4H, m), 1.5 (2H, br s), 2.3 (1H, dd), 2.55 (3H, d), 2.7-2.8 (2H, m), 2.85 (2H, dd), 3.2-3.4 (4H, m), 3.5-3.6 (2H, m), 3.6-3.8 (2H, m), 3.82-3.90 (3H, m), 4.8 (1H, quartet), 5.0 (2H, s), 5.05 (1H, br d), 5.5 (1H, d), 6.1 (2H, s), 6.8-6.9 (3H, m), 7.0-7.1 (3H, m), 7.15-7.40 (7H, m); MS: 798 (MH⁺)

Example 145

(3*S*)-Tetrahydro-3-furanyl *N*-((1*S*, 2*R*)-1-[(4-benzyloxy)benzyl-3-[2,2-dimethyl-5-(*N'*-methylcarbamoyloxy)-pentyl] [(3,4-methylenedioxyphenyl)sulfonyl] amino-2-hydroxypropyl) carbamate (362)

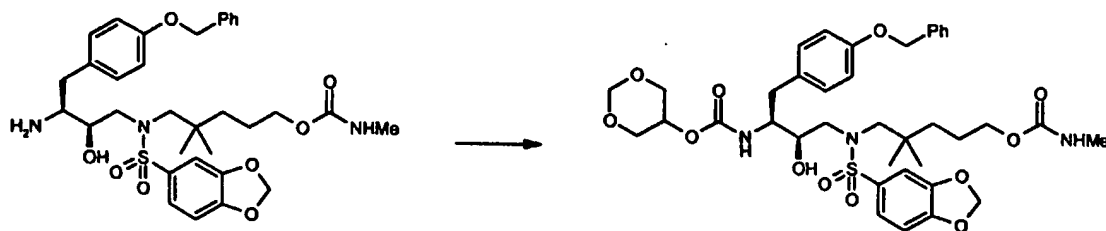


Treatment of the product from step 6 (Example 361) with (3*S*)-tetrahydro-3-furanyl *N*-succinimidyl carbonate as described in step g (example 801) provided the title compound as a solid foam; ¹H NMR (DMSO-*d*₆): 0.8 (6H, d),

1.05-1.10 (2H, m), 1.4-1.5 (2H, m), 1.7 (1H, br s), 1.95-2.05 (1H, m), 2.4 (1H, t), 2.55 (3H, d), 2.8 (2H, t), 2.9 (1H, dd), 3.2-3.35 (3H, m), 3.5-3.5 (4H, m), 3.8 (2H, br s), 4.9-5.0 (4H, m), 5.7 (1H, s), 6.2 (2H, s), 6.8-6.9 (3H, m), 7.00-7.15 (4H, m), 7.2-7.4 (7H, m); MS: 756 (MH+)

Example 146

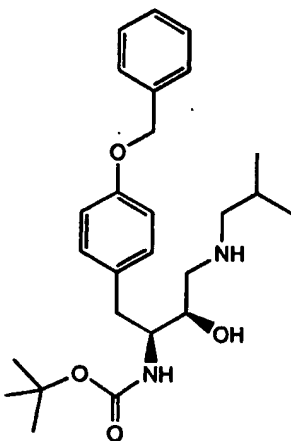
1,3-Dioxan-5-yl *N*-((1*S*,2*R*)-1-[(4-benzyloxy)benzyl-3-[2,2-dimethyl-5-(*N'*-methylcarbamoyloxy)-pentyl][(3,4-methylenedioxyphenyl)sulfonyl]amino-2-hydroxypropyl)carbamate (363)



Treatment of the product from step 6 (example 361) with 1,3-dioxan-5-yl *p*-nitrophenyl carbonate as described in step 7 (example 627) provided the title compound as a solid foam; ¹H NMR (DMSO-*d*₆): 0.8 (6H, s), 1.1-1.3 (2H, m), 1.4-1.5 (2H, m), 2.4 (1H, t), 2.55 (3H, d), 2.75-2.85 (2H, m), 2.9 (1H, dd), 3.20-3.35 (2H, m), 3.45 (1H, d), 3.6-3.9 (6H, m), 4.3 (1H, br s), 4.65 (1H, br d), 4.75 (1H, br d), 4.9-5.0 (3H, m), 5.7 (1H, s), 6.1 (2H, s), 6.75-6.85 (3H, m), 6.95-7.05 (3H, m), 7.2-7.4 (8H, m); MS: 772 (MH+);

Step 1:

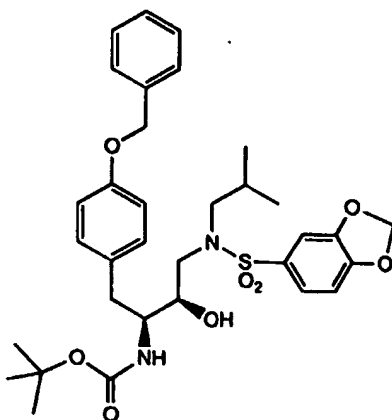
t-Butyl-(1S,2R)-1-(4-benzyloxy-benzyl)-3-i-butylamino-2-hydroxypropyl-carbamate



- 5 i-Butylamine (10.0 g, 137 mmol) was added to a solution of t-Butyl-(1S,2R)-1-(4-benzyloxy-benzyl)-2,3-epoxydo-propyl-carbamate (7.0 g, 18.9 mmol) (prepared according to the reference by Chen, P. at all., *Tetrahedron Letters*, Vol 38. p3175-8, 1997), in 100 ml i-propanol.
- 10 The mixture was stirred at 85°C for 2 hours, then it was cooled to 5°C and 500 ml water was added dropwise. The resulting suspension was stirred for 30 minutes at 5°C, then filtered. The solid was washed with water (3x100 ml) then dried under reduced pressure to obtain 8.3 g (99 %) title compound. ¹H -NMR: (CDCl₃): 0.88 (6H,d), 1.34 (9H, s), 1.68 (1H,m), 2.38 (2H,d), 2.64 (2H,d), 2.80 (1H,m), 2.86 (1H,dd), 3.40 (1H,m), 3.70 (2H, s(broad)), 4.63 (1H,d), 5.01 (2H,s), 6.88 (2H,d), 7.12 (2H,d), 7.40 (5H,m).

20 Step 2:

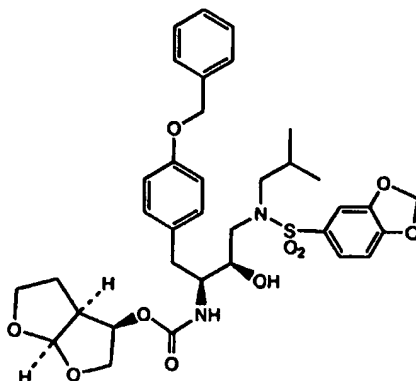
t-Butyl-N((1S,2R)-1-(4-benzyloxy-benzyl)-3-i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl)-carbamate



5

A solution of the product from Step 1 (8.3 g, 18.8 mmol), 3,4-methylenedioxysulfonylchloride (5.0 g, 22.7 mmol) and diisopropylethylamine (5.0 g, 38.7 mmol) stirred at 20°C for 4 hours. 200 ml water was then added to the reaction mixture and the phases were separated. The aqueous phase was extracted with dichloromethane (3x100 ml), then the organic phases were combined; dried with magnesium sulfate, filtered and concentrated. The residue was dissolved in 300 ml ether, 50 g silicagel was added to the solution, then the mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was mixed with 300 ml hexane. The mix was stirred for three hours at 20°C, then the solid was filtered and dried to afford 10.9 g (93 %) title compound. ¹H NMR (CDCl₃): 0.85 (3H,d), 0.88 (3H,d), 1.34 (9H,s), 1.82 (1H,m), 3.04 (2H,m), 3.68 (1H,s(broad)), 3.75 (1H,s(broad)), 3.86 (1H,s), 4.60 (1H,d), 5.02 (2H,s), 6.04 (2H,s), 6.88 (3H,m), 7.15 (3H,m), 7.35 (6H,m).

20



Step 3:

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(4-benzyloxy-benzyl)-3-1-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl)-carbamate (364)

100 ml trifluoroacetic acid was added dropwise to a solution of the product from Step 2 (10.2g, 16.3 mmol) in 200 ml dichloromethane. The mixture was stirred for 1
 10 hour at 20°C, then the solvents were evaporated under reduced pressure. The residue was dissolved in 200 ml dichloromethane and 300 ml 5% aqueous sodium carbonate solution was added, then the mixture was stirred at 20°C for 15 minutes. Phases were separated, then the aqueous
 15 phase was extracted with additional (2x100 ml) dichloromethane. Organic phases were combined then concentrated under reduced pressure. The residue was dissolved in 150 ml acetonitrile. Diisopropylethylamine (8.0 g, 62 mmol) and (3R,3aS,6aR)-Hexahydrofuro[2,3-
 20 b]furan-3-yl-4-nitrophenyl carbonate (8.0 g, 27.1 mmol) was added, and the solution was stirred for 12 hours at 20°C. 10 ml 25% aqueous ammonium hydroxide solution was added, then the mixture was stirred for an additional hour. The solvents were removed under reduced pressure,

the residue dissolved in 500 ml ether, and the solution was extracted with 5% sodium carbonate solution (10x100 ml). The organic phase was dried with anhydrous sodium carbonate, filtered and concentrated under reduced pressure. 20 ml ether was added to the residue, then after a small amount of solid formation 200 ml hexane was added, and the mixture was stirred at 20°C for 1 hour, then filtered and dried, to obtain 11.3 g (quant.) title compound. ¹H NMR (DMSO-d₆): 0.76 (3H,d), 0.82 (3H,d), 1.2 (1H,m), 1.35 (1H,m), 1.92 (1H,m), 2.35 (1H,t), 2.70 (3H,m), 2.85-3.05 (2H,m), 3.45 (1H,m), 3.55 (3H,m), 3.66 (1H,t), 3.80 (1H,dd), 4.81 (1H,m), 5.00 (3H,s(broad)), 5.47 (1H,d), 6.13 (2H,s), 6.82 (2H,d), 7.06 (3H,m), 7.20-7.40 (7H,m); MS: 682 (M+).

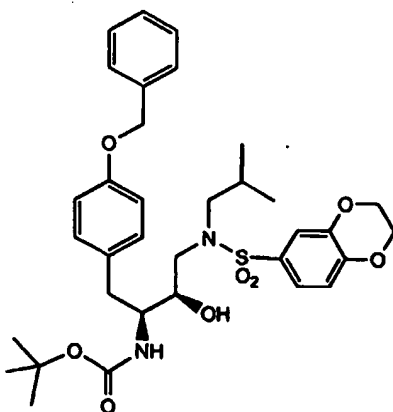
15

Example 148

Step 1:

t-Butyl-N((1S,2R)-1-(4-benzyloxy-benzyl)-3-i-butyl-[(3,4-ethylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl)-carbamate

20

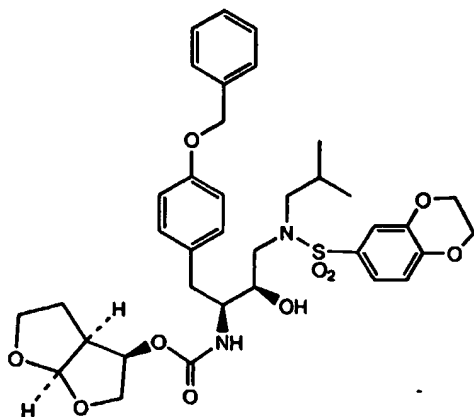


The reaction was carried out as described in Step 2, Example 147, except 3,4-ethylenedioxyphenyl sulfonylchloride was used in the reaction (83%).

¹H NMR (CDCl₃): 0.86 (3H,d), 0.89 (3H,d), 1.34 (9H,s),
 5 1.82 (1H,m), 2.85 (4H,m), 3.04 (2H,m), 3.69
 (1H,s(broad)), 3.76 (1H,s(broad)), 3.91 (1H,s), 4.27 (4H,
 m), 4.61 (1H,d), 5.03 (2H,s), 6.89 (2H,d), 6.93 91H,d),
 7.14 (2H,d), 7.20-7.45 (7H, m).

Step 2:

10 (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-(
 (4-benzyloxy-benzyl)-3-i-butyl-[(3,4-
 ethylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl-
 caramate (365)



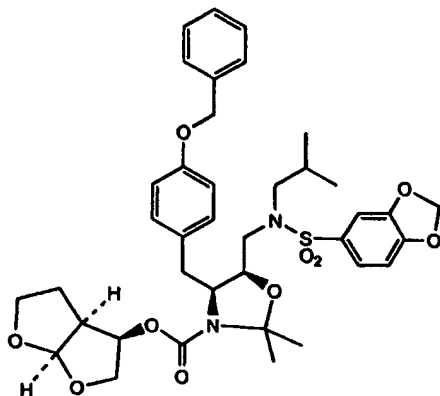
15 The reaction was carried out as described in Step3,
 Example 147 except the product from Step 1, Example 144
 was used in the reaction (43%). ¹H NMR (DMSO-d₆): 0.78
 (3H,d), 0.84 (3H,d), 1.20 (1H,m), 1.35 (1H,m), 1.95
 (1H,m), 2.37 (1H,t), 2.70 (3H,m), 2.95 (2H,m), 3.45
 20 (1H,m), 3.58 (3H,m), 3.68 (1H,t), 3.82 (1H,m), 4.28
 (4H,d), 4.82 (1H,m), 5.01 (3H, s+m), 5.48 (1H,d), 6.84

(2H,d), 7.02 (1H,d), 7.08 (2H, d), 7.20-7.40 (7H,m); MS: 696 (M+).

Example 149

5 Step 1:

N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-oxycarbonyl-, (4S,5R)-4-(4-benzyloxy-benzyl)-5-i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-dimethyl-oxazolidine



10

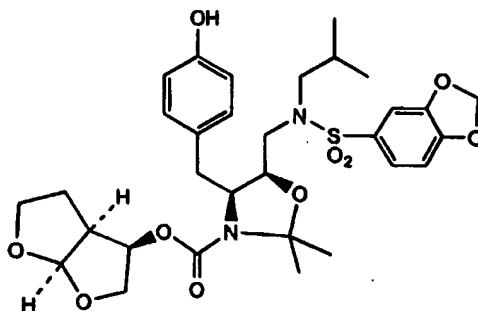
2,2-dimethoxy-propane (20 g, 192 mmol) and p-toluenesulfonic acid (1.0 g, 5.8 mmol) was added to the solution of the product of Example 630 (11.3 g, 16.5 mmol) in 200 ml dichloromethane. The solution was
15 refluxed for 4 hours; then cooled to 20°C. The mixture was extracted with 5% sodium carbonate solution, then the organic phase was dried with magnesium sulfate, filtered and concentrated under reduced pressure. The residue was purified on silicagel using hexane-ethyl acetate (1:1) as
20 eluent, to provide 7.78 g (60 %) title compound. ¹H NMR (CDCl₃): 0.83 (3H,d), 0.91 (3H,d), 1.40, 1.48 (3H,s)*, 1.56, 1.64 (3H,s)*, 1.85 (2H,m), 2.0 (1H,m), 2.70 (3H,m),

2.80 (1H,m), 3.00 (3H,m), 3.40 (2H,m), 3.80 (2H,m), 3.95 (1H,m), 4.20 (1H,m), 4.30 (1H,m), 4.89 (1H,dd), 5.03 (2H,s), 5.65, 5.68 (1H,d)*, 6.00 (2H,s), 6.79 (1H,d), 6.89 (2H,d), 7.02 (2H,d), 7.10 (1H,m), 7.30-7.45 (6H,m).

5 *: possible indication for rotamers.

Step 2:

N- (3R,3aS,6aR) -Hexahydrofuro[2,3-b]furan-3-yl-oxycarbonyl-, (4S,5R) -4- (4-hydroxybenzyl) -5-1-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-dimethyl-oxazolidine (366)



8 g palladium (on charcoal, 10% Pd, Degussa type) was added to a stirred solution of the product of Step 1 (7.7 g, 10.6 mmol) in 400 ml tetrahydrofuran. The mixture was stirred under atmospheric pressure of hydrogen for 12 hours. The catalyst was filtered, and the solvent was removed under reduced pressure.

The residue was stirred for 2 hours in 200 ml hexane, then the solid was filtered, washed with hexane (2x20 ml) to obtain 6.4 g (95 %) title compound. ¹H NMR (CDCl₃): 0.83 (3H,d), 0.91 (3H,d), 1.41, 1.48 (3H,s)*, 1.56, 1.65 (3H,s)*, 1.85 (2H,m), 2.00 (1H,m), 2.60-3.10 (6H,m), 3.40 (2H,m), 3.70-4.35 (6H,m), 4.90 (1H, dd), 5.05-5.30

(2H,m), 5.66, 5.69 (1H,d)*, 6.06 (2H,s), 6.75 (2H,d),
6.83 (1H,d), 6.97 92H,d), 7.00-7.15 (2H,m); MS: 632 (M+).

*: possible indication for rotamers.

5

Example 150

Step 1:

General procedure for the aralkylation of N-(3R,3aS,6aR)-
Hexahydrofuro[2,3-b]furan-3-yl-oxycarbonyl-, (4S,5R)-4-
(4-hydroxybenzyl)-5-i-butyl-[(3,4-methylenedioxyphenyl)
10 sulfonyl]-aminomethyl-2,2-Dimethyl-oxazolidine

0.5 mmol aralkyl halide[1] was added to a stirred mixture
of N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-
oxycarbonyl-, (4S,5R)-4-(4-hydroxybenzyl)-5-i-butyl-
[(3,4-methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-
15 Dimethyl-oxazolidine (126 mg, 0.2 mmol) and cesium
carbonate (250 mg, 0.76 mmol) in 2 ml N,N-
dimethylformamide. The mixture was stirred at the
indicated temperature[2] for indicated number of hours[3]
then diluted with 100 ml ether at 20°C. The mixture was
20 filtered, and the filtrate was extracted with water
(10x20 ml). The organic phase was dried with magnesium
sulfate, filtered and concentrated under reduced pressure
to obtain the following compounds:

N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-
25 oxycarbonyl-, (4S,5R)-4-{4-[3-(4-fluorophenyl)-1-

propyloxy]-benzyl}-5-i-butyl-[(3,4-methylenedioxyphenyl)
sulfonyl]-aminomethyl-2,2-dimethyl-oxazolidine

5

[1]: 1-chloro-3-(4-fluorophenyl)-propane; [2]: 60°C; [3]:
6 hours; MS: 768 (M+).

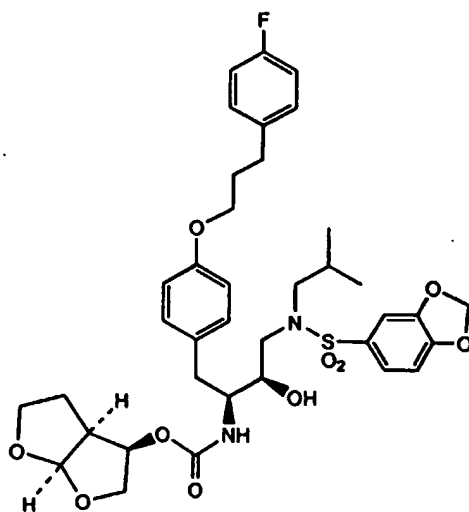
Step 2:

General procedure for the deprotection of N-(3R,3aS,6aR)-
10 Hexahydrofuro[2,3-b]furan-3-yl-oxycarbonyl-, (4S,5R)-4-
(4-aralkyloxybenzyl)-5-i-butyl-[(3,4-
methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-Dimethyl-
oxazolidine (the product of Step 1.)

4 M HCl in dioxane (7.5 ml) and water (0.2 g) was added
15 to a stirred solution of the product of Step 1 in 15 ml
dioxane. The solution was stirred for 5 hours, then the
solvents were removed under reduced pressure. The residue
was dissolved in 100 ml ethyl acetate, washed with 5%
aqueous sodium bicarbonate solution, then the organic
20 phase dried with magnesium sulfate. The solvents were
removed and the residue was purified either with
filtration from silicagel slurry and crystallization(a)

or silicagel chromatography(b), using the eluent(s) as indicated [1] to obtain the following compounds (yield: [2]):

- 5 (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-{4-[3-(4-fluorophenyl)-1-propyloxy]-benzyl}-3-i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl-carbamate (366)



- 10 [1]: b, Hexane-EtOAc (1:1) then Hexane-EtOAc (1:2); [2] : 36 %. ¹H-NMR (DMSO-*d*₆): 0.76 (3H,d), 0.81 (3H,d), 1.15 (1H,m), 1.31 (1H,m), 1.93 (3H,m), 2.34 (1H,t), 2.68 (5H,m), 2.85-3.00 (3H,m), 3.40-3.90 (8H,m), 4.81 (1H,dd), 4.98 (1H,d), 5.47 (1H,d), 6.13 (2H,s), 6.74 (2H,d), 7.04 (4H,m), 7.20 (4H,m), 7.27 (1H,d); MS: 728 (M+).

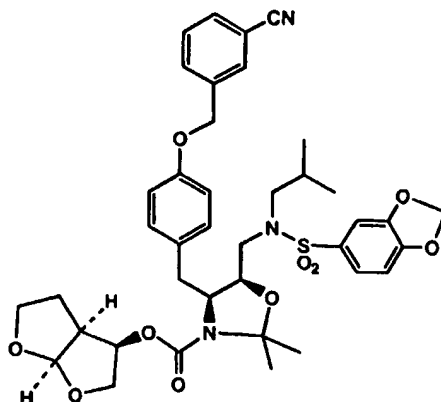
15

Example 151

Step 1:

N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-oxycarbonyl-, (4S,5R)-4-[4-(3-cyanobenzyloxy)-benzyl]-5-

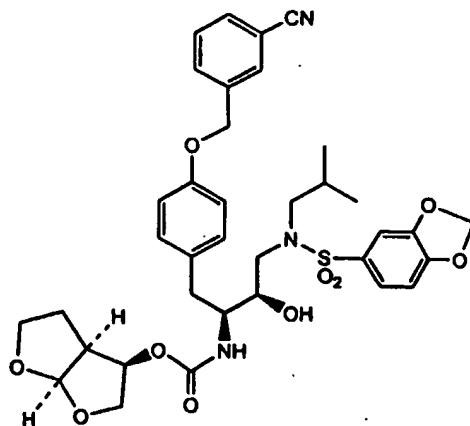
**i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-aminomethyl-
2,2-dimethyl-oxazolidine**



- 5 [1]: 3-cyanobenzyl bromide; [2]: 20°C; [3]: 1 hour; MS:
747 (M+).

Step 2:

- (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-
10 [4-(3-cyanobenzyloxy)-benzyl]-3-i-butyl-[(3,4-
methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl-
carbamate (367)



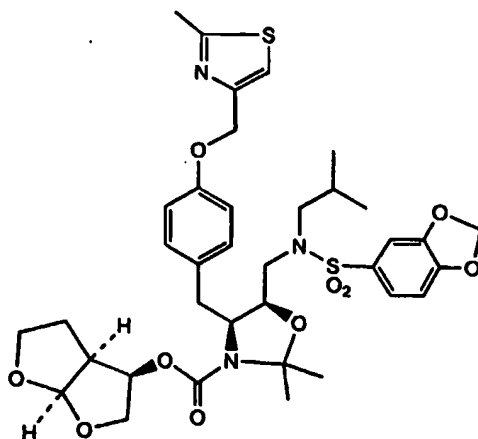
[1]: b, Hexane-EtOAc (1:1) then Hexane-EtOAc (1:2); [2]:
46 %. ¹H NMR (DMSO-d₆): 0.75 (3H,d), 0.81 (3H,d), 1.19
(1H,m), 1.31 (1H,m), 1.92 (1H,m), 2.35 (1H,t), 2.41
(3H,m), 2.85-3.00 (3H,m), 3.40-3.60 (5H,m), 3.65 (1H,t),
5 3.80 (1H,dd), 4.81 (1H,dd), 4.99 (1H,d), 5.07 (2H,s),
5.47 (1H,d), 6.13 (2H,s), 6.83 (2H,d), 7.04 (3H,m), 7.20
(2H,m), 7.27 (1H,d), 7.56 (1H,t), 7.75 (2H,t), 7.85 (1H,
s); MS: 707 (M+).

10

Example 152

Step 1:

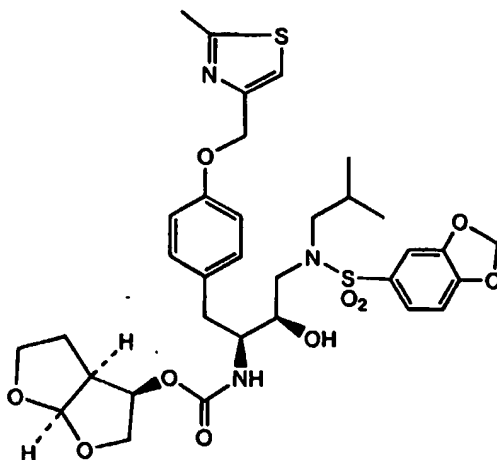
N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-
oxycarbonyl-, (4S,5R)-4-[4-(2-methylthiazolo-4-
methyloxy)-benzyl]-5-*i*-butyl-[(3,4-
15 methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-dimethyl-
oxazolidine



[1]: 4-chloromethyl-2-methylthiazole hydrochloride; [2]:
20 70°C; [3]: 5 hour; MS: 743 (M+).

Step 2:

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-[4-(2-methylthiazolo-4-methyloxy)-benzyl]-3-i-butyl-
 5 [(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl-carbamate (368)



[1]: b, EtOAc (neat); [2]: 36 %. ¹H NMR (DMSO-d₆): 0.76 (3H,d), 0.82 (3H,d), 1.20 (1H,m), 1.33 (1H,m), 1.92 (1H,m), 2.35 (1H,t), 2.61 (3H,s), 2.65 (3H,m), 2.85-3.00 (3H,m), 3.40-3.60 (5H,m), 3.68 (1H,t), 3.80 (1H,dd), 4.81 (1H,dd), 4.99 (3H,s(broad)), 5.47 (1H,d), 6.13 (2H,s), 6.83 (2H,d), 7.06 (3H,m), 7.20 (2H,m), 7.27 (1H,d), 7.47 (1H,s); MS: 703 (M⁺).

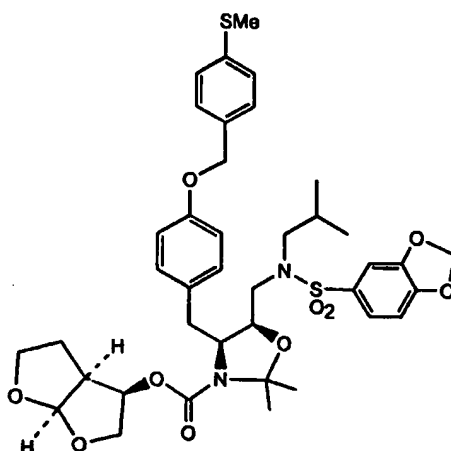
15

Example 153

Step 1:

N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-oxycarbonyl-, (4S,5R)-4-[4-(4-methylthio-benzyloxy)-

benzyl]-5-*i*-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-
aminomethyl-2,2-dimethyl-oxazolidine

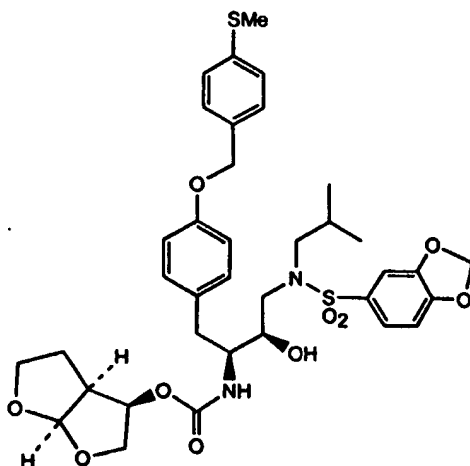


5

[1]: 4-methylthiobenzylchloride; [2]: 40°C; [3]: 4 hour;
MS: 768 (M+).

Step 2:

- 10 (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-[4-(4-methylthio-benzyloxy)-benzyl]-3-*i*-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl)-carbamate (369)



-309-

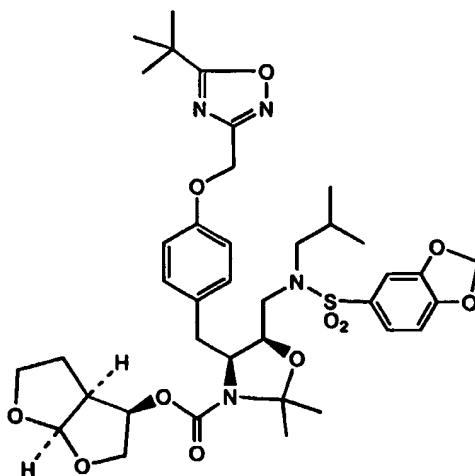
[1]: b, Hexane-EtOAc (1:1) then Hexane-EtOAc (1:2); [2]:
 17 %. ¹H NMR (DMSO-d₆): 0.75 (3H,d), 0.81 (3H,d), 1.20
 (1H,m), 1.30 (1H,m), 1.92 (1H,m), 2.35 (1H,t), 2.42
 5 (3H,s), 2.70 (3H,m), 2.85-3.00 (3H,m), 3.45 (1H,m), 3.55
 (3H,m), 3.66 (1H,t), 3.80 (1H,dd), 4.81 (1H,dd), 4.98
 (3H,s+m), 5.47 (1H,d), 6.12 (2H,s), 6.80 (2H,d), 7.05
 (3H,m), 7.15-7.35 (6H,m); MS: 728 (M+).

10

Example 154

Step 1:

**N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-
 oxycarbonyl-, (4S,5R)-4-[4-(5-t-butyl-1,2,4-oxadiazolo-3-
 methyloxy)-benzyl]-5-i-butyl-[(3,4-
 15 methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-dimethyl-
 oxazolidine**

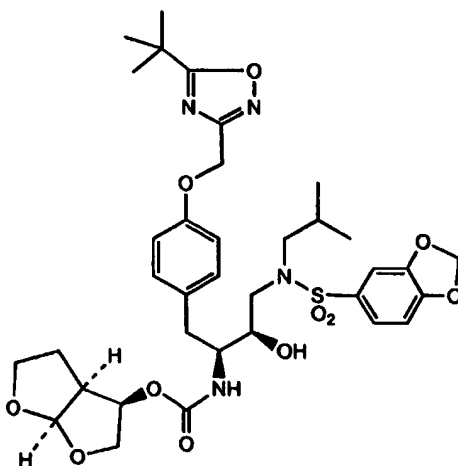


[1]: 5-t-butyl-3-chloromethyl-1,2,4-oxadiazole; [2]:
 20°C; [3]: 12 hour; MS: 770 (M+).

-310-

Step 2:

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-[4-(5-t-butyl-1,2,4-oxadiazolo-3-methyloxy)-benzyl]-3-i-
 5 butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl)-carbamate (370)



[1]: b, Hexane-EtOAc (1:1) then Hexane-EtOAc (1:2); [2] :
 10 56 %. ¹H NMR (DMSO-d₆): 0.76 (3H,d), 0.83 (3H,d), 1.19
 (1H,m), 1.30 (1H,m), 1.36 (9H,s) 1.93 (1H,m), 2.37
 (1H,t), 2.72 (3H,m), 2.90-3.02 (3H,m), 3.42-3.60 (4H,m),
 3.68 (1H,t), 3.82 (1H,dd), 4.81 (1H,dd), 5.0
 (1H,s(broad)), 5.12 (2H,s), 5.47 (1H,d), 6.13 (2H,s),
 15 6.85 (2H,d), 7.03 (1H,d), 7.10 (2H,d), 7.20 (2H,d), 7.28
 (1H,d); MS: 730(M+).

Example 155

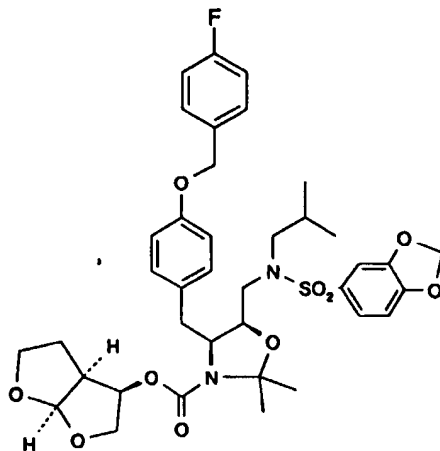
Step 1:

N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-
 20 oxycarbonyl-, (4S,5R)-4-[4-(4-fluorobenzyloxy)-benzyl]-5-

-311-

i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-dimethyl-oxazolidine (371)

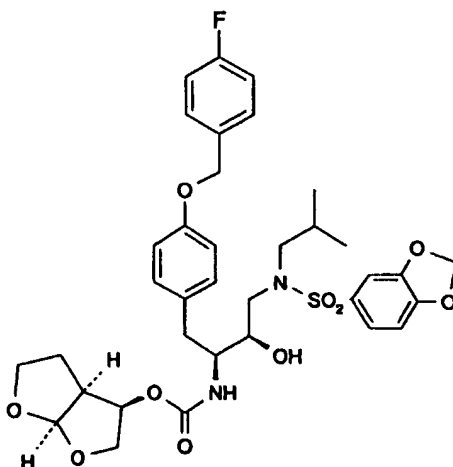
[1]: 4-fluorobenzylbromide; [2]: 20°C; [3]: 1 hour; MS:



741 (M+).

5 Step 2:

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-[4-(4-fluorobenzoyloxy)-benzyl]-3-i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl)-carbamate (371)



10 [1]: a, Hexane-EtOAc (1:1); [2] :41 %. ¹H-NMR (DMSO-d₆): 0.75 (3H,d), 0.81 (3H,d), 1.18 (1H,m), 1.31 (1H,m), 1.90 (1H,m), 2.34 (1H,t), 2.62-2.74 (3H,m), 2.89-3.02 (2H,m),

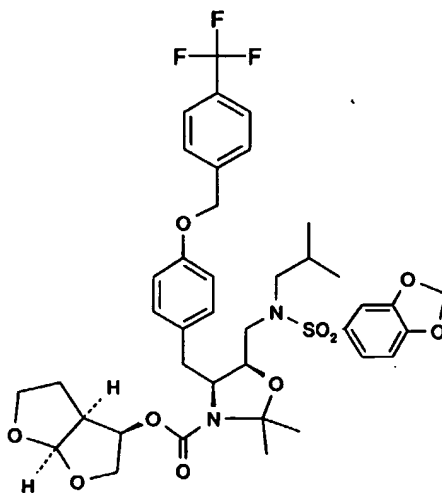
-312-

3.40-3.49 (1H,m), 3.50-3.60 (3H,m), 3.65 (1H,m), 3.80
 (1H,dd), 4.80 (1H,dd), 4.97 (2H,s(broad)), 4.99 (1H,d),
 5.46 (1H,d), 6.12 (2H,s), 6.81 (2H,d), 7.02 (1H,d), 7.06
 (2H,d), 7.15 (1H,d), 7.18-7.23 (3H,m), 7.27 (1H,dd), 7.43
 5 (2H,dd); MS: 701 (M+).

Example 156

Step 1:

**N- (3R,3aS,6aR) -Hexahydrofuro[2,3-b]furan-3-yl-
 oxycarbonyl-, (4S,5R) -4- [4- (4-trifluoromethylbenzyloxy) -
 10 benzyl] -5-i-butyl- [(3,4-methylenedioxyphenyl) sulfonyl] -
 aminomethyl-2,2-dimethyl-oxazolidine**



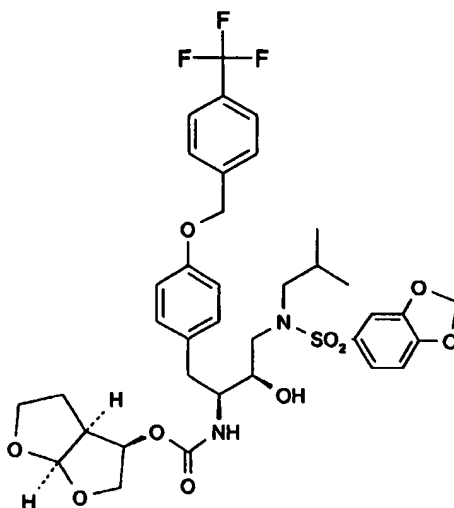
[1]: 4-trifluoromethylbenzylbromide; [2]: 20°C; [3]: 1
 hour; MS: 791 (M+).

15

Step 2:

-313-

(3R,3aS,6aR) -Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R) -1-[4-(4-trifluoromethylbenzyloxy)-benzyl]-3-1-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl)-carmamate (372)



5

[1]: a, Hexane-EtOAc (1:1); [2] : 47 %. ¹H-NMR (DMSO-*d*₆): 0.75 (3H,d), 0.81 (3H,d), 1.16 (1H,m), 1.26 (1H,m), 1.91 (1H,m), 2.34 (1H,t), 2.65-2.76 (3H,m), 2.89-3.00 (2H,m), 3.45 (1H,m), 3.54 (3H,m), 3.63 (1H,m), 3.79 (1H,dd), 4.80 (1H,dd), 4.99 (1H,d), 5.12 (2H,s(broad)), 5.44 (1H,d), 6.12 (2H,s), 6.83 (2H,d), 7.02 (1H,d), 7.07 (2H,d), 7.21 (2H,d), 7.27(1H,d), 7.60 (2H,d), 7.70 (2H,d); MS: 751(M⁺).

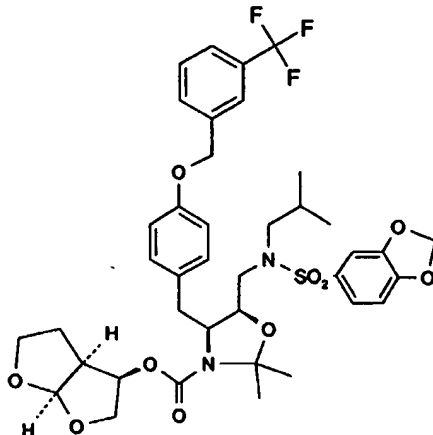
10

Example 157

15 Step 1:

-314-

N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-oxycarbonyl-, (4S,5R)-4-[4-(3-trifluoromethylbenzyloxy)-benzyl]-5-i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-dimethyl-oxazolidine

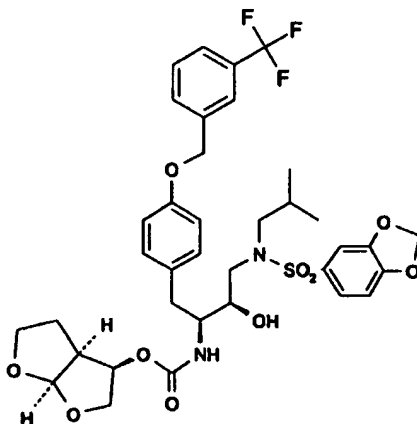


5

[1]: 3-trifluoromethylbenzylbromide; [2]: 20°C; [3]: 1 hour; MS: 791 (M+).

Step 2:

(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-[4-(3-trifluoromethylbenzyloxy)-benzyl]-3-i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl)-carbamate (373)



-315-

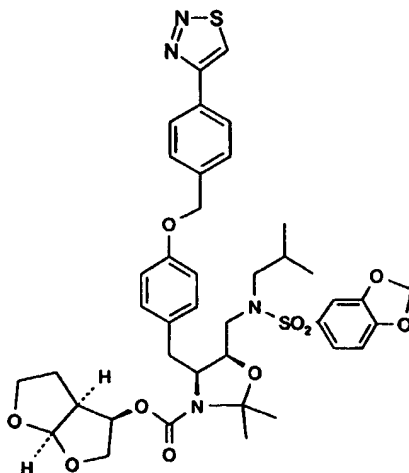
[1]: a, Hexane-EtOAc (1:1); [2]: 47 %. ¹H-NMR (DMSO-d₆):
0.75 (3H,d), 0.81 (3H,d), 1.15-1.22 (1H,m), 1.30 (1H,m),
1.91 (1H,m), 2.34 (1H,t), 2.65-2.75 (3H,m), 2.89-3.01
(2H,m), 3.45 (1H,m), 3.52-3.59 (3H,m), 3.64 (1H,m), 3.80
5 (1H,dd), 4.80 (1H,dd), 4.99 (1H,d), 5.11 (2H,s(broad)),
5.45 (1H,d), 6.12 (2H,s), 6.84 (2H,d), 7.03 (1H,d), 7.07
(2H,d), 7.21 (2H,m), 7.27 (1H,dd), 7.58 (1H,t), 7.65
(1H,d), 7.70 (1H,d), 7.74 (1H,s); MS: 751(M+).

10

Example 158

Step 1:

**N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-
oxycarbonyl-, (4S,5R)-4-[4-(1,2,3-thiadiazole-4-
benzyloxy)-benzyl]-5-i-butyl-[(3,4-
15 methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-dimethyl-
oxazolidine**

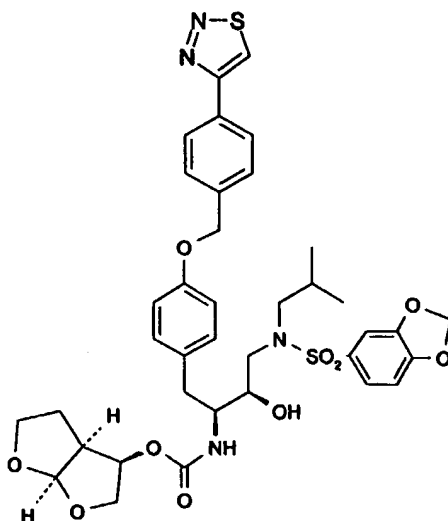


-316-

[1]: 4-[4-(bromomethyl)phenyl]-1,2,3-thiadiazole; [2]:
20°C; [3]: 1 hour; MS: 807 (M+).

Step 2:

- 5 (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-[4-(1,2,3-thiadiazole-4-benzyloxy)-benzyl]-3-*i*-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-amino-2-hydroxypropyl)-carbamate (374)



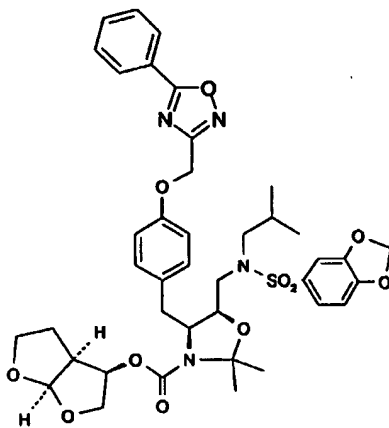
- 10 [1]: a, Hexane-EtOAc (1:3); [2]: 54 %. ¹H NMR (DMSO-*d*₆):
0.77 (3H,d), 0.83 (3H,d), 1.20 (1H,m), 1.31 (1H,m), 1.93
(1H,m), 2.37 (1H,t), 2.67-2.77 (3H,m), 2.91-3.03 (2H,m),
3.48 (1H,m), 3.53-3.61 (3H,m), 3.67 (1H,m), 3.81 (1H,dd),
4.82 (1H,dd), 5.00 (1H,m), 5.11 (2H,s(broad)), 5.43
15 (1H,d), 6.14 (2H,s), 6.87 (2H,d), 7.04 (1H,d), 7.10
(2H,d), 7.22 (2H,m), 7.29 (1H,d), 7.58 (2H,d), 8.13
(2H,d), 9.59 (1H,s); MS: 767(M+).

Example 159

-317-

Step 1:

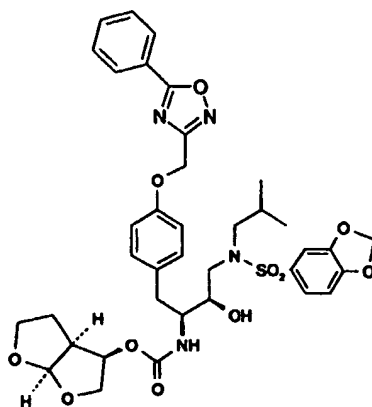
N- (3R,3aS,6aR) -Hexahydrofuro [2,3-b] furan-3-yl-oxycarbonyl-, (4S,5R) -4- [4- (5-phenyl-1,2,4-oxadiazolo-3-methyloxy) -benzyl] -5-i-butyl- [(3,4-
5 methylenedioxyphenyl) sulfonyl] -aminomethyl-2,2-dimethyl-oxazolidine



[1]: 3-chloromethyl-5-phenyl-1,2,4-oxadiazole; [2]: 20°C;
 [3]: 24 hour; MS: 791 (M+).

10 Step 2:

(3R,3aS,6aR) -Hexahydrofuro [2,3-b] furan-3-yl-N((1S,2R) -1- [4- (5-phenyl-1,2,4-oxadiazolo-3-methyloxy) -benzyl] -3-i-butyl- [(3,4-methylenedioxyphenyl) sulfonyl] -amino-2-hydroxypropyl-carbamate (375)



-318-

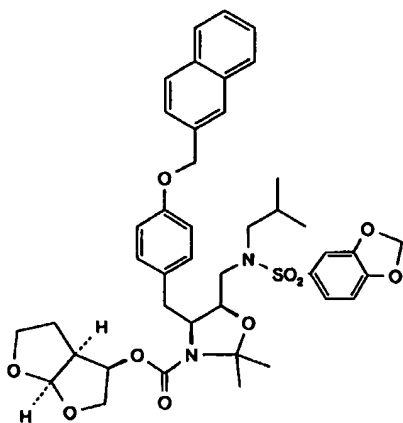
[1]: a, Hexane-EtOAc (1:3); [2]: 53 %. ^1H NMR ($\text{DMSO}-d_6$): 0.77 (3H,d), 0.84 (3H,d), 1.18 (1H,m), 1.32 (1H,m), 1.94 (1H,m), 2.38 (1H,t), 2.68-2.78 (3H,m), 2.93-3.04 (2H,m), 3.46-3.60 (4H,m), 3.69 (1H,m), 3.81 (1H,dd), 4.82 (1H,dd), 5.01 (1H,m), 5.27 (2H,s(broad)), 5.42 (1H,d), 6.14 (2H,s), 6.91 (2H,d), 7.05 (1H,d), 7.12 (2H,d), 7.23 (2H,d), 7.29 (1H,d), 7.62 (2H,m), 7.71 (1H,m), 8.10 (2H,d); MS: 751 (M+).

10

Example 160

Step 1:

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (4S,5R)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 2,2-dimethyl-4-[4-(2-naphthylmethoxy)benzyl]-1,3-
 15 oxazolidine-3-carboxylate



[1]: 2-(bromomethyl)naphthalene; [2]: 20°C; [3]: 12 hour;
 MS: 773 (M+).

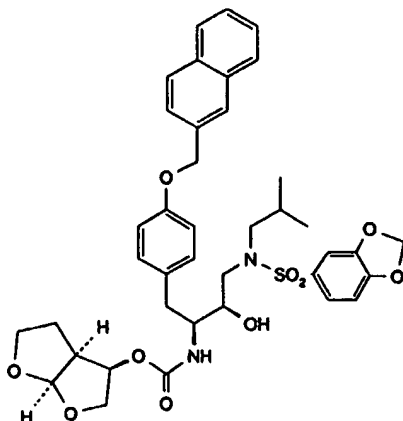
20

Step 2:

-319-

(3*R*, 3*aS*, 6*aR*) -hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*) -3-
 [(1,3-benzodioxol-5-ylsulfonyl) (isobutyl) amino] -2-hydroxy
 -1-[4-(2-naphthylmethoxy)benzyl]propylcarbamate (376)

5



[1]: c, Et₂O; [2] (Calc. from the product of Procedure 7):
 10 92 %.

¹H NMR (DMSO-*d*₆): δ 0.74 (3H,d), 0.80 (3H,d), 1.16 (1H,m),
 1.25 (1H,m), 1.91 (1H,m), 2.33 (1H,t), 2.64-2.73 (3H,m),
 2.88-2.99 (2H,m), 3.44 (1H,m), 3.50-3.56 (3H,m), 3.62
 15 (1H,m), 3.77 (1H,dd), 4.78 (1H,dd), 4.97 (1H, s(broad))
 5.16 (2H,s), 5.40 (1H,d), 6.11 (2H,s), 6.86 (2H,d), 7.01
 (1H,d), 7.06 (2H,d), 7.19 (2H,m), 7.26 (1H,d), 7.46
 (2H,m), 7.50 (1H,d), 7.88 (3H,m); MS: 733 (M⁺).

20

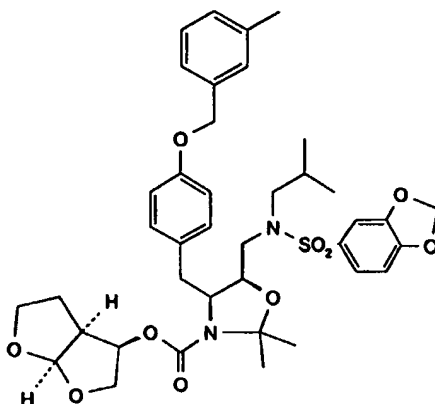
Example 161

Step 1:

-320-

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 2,2-dimethyl-4-{4-[(3-methylbenzyl)oxy]benzyl}-1,3-
 oxazolidine-3-carboxylate

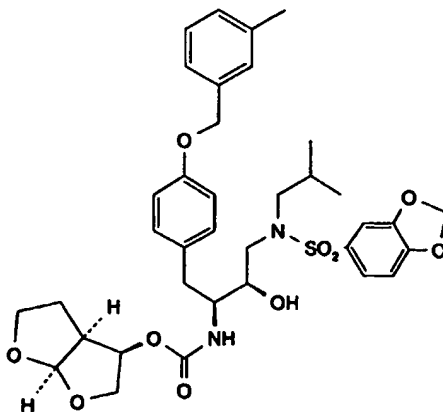
5



[1]: 3-bromomethyltoluene; [2]: 20°C; [3]: 12 hour; MS:
 10 737 (M⁺).

Step 2:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy
 15 -1-{4-[(3-methylbenzyl)oxy]benzyl}propylcarbamate (377)



-321-

[1]: c, Et₂O; [2]: 72 %.

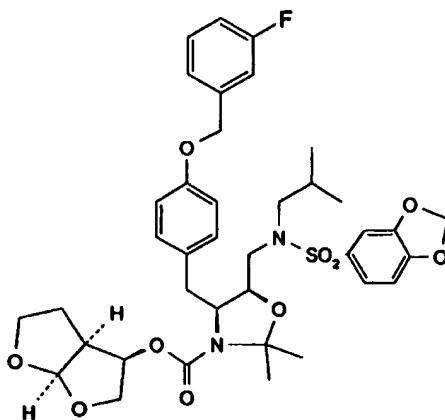
¹H NMR (DMSO-*d*₆): δ 0.74 (3H,d), 0.80 (3H,d), 1.16 (1H,m),
 1.28 (1H,m), 1.90 (1H,m), 2.25 (3H,s), 2.33 (1H,t), 2.64-
 5 2.73 (3H,m), 2.88-2.99 (2H,m), 3.44 (1H,m), 3.51-3.57
 (3H,m), 3.64 (1H,m), 3.79 (1H,dd), 4.80 (1H,dd), 4.93
 (2H,s), 4.97 (1H,s(broad)), 5.45 (1H,d), 6.11 (2H,s),
 6.79 (2H,d), 7.00-7.08 (4H,m), 7.14-7.22 (4H,m), 7.25-
 7.27 (1H,m); MS: 697(M⁺).

10

Example 162

Step 1:

15 (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 4-{4-[(3-fluorobenzyl)oxy]benzyl}-2,2-dimethyl-1,3-
 oxazolidine-3-carboxylate



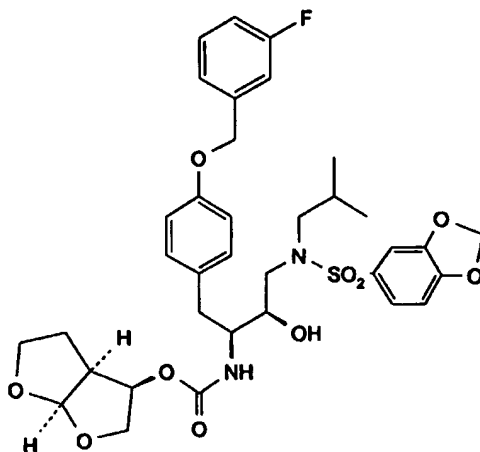
20

[1]: 3-fluorobenzylbromide; [2]: 20°C; [3]: 12 hour; MS:
 741 (M⁺).

-322-

Step 2:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-{4-[(3-
 5 fluorobenzyl)oxy]benzyl}-2-hydroxypropylcarbamate (378)



[1]: c, Et₂O; [2]: 67 %.

¹H NMR (DMSO-*d*₆): δ 0.74 (3H,d), 0.80 (3H,d), 1.19 (1H,m),
 10 1.25-1.33 (1H,m), 1.81-1.92 (1H,m), 2.33 (1H,t), 2.64-
 2.73 (3H,m), 2.88-3.00 (2H,m), 3.44 (1H,m), 3.51-3.58
 (3H,m), 3.64 (1H,m), 3.79 (1H,dd), 4.80 (1H,dd), 4.98
 (1H,d) 5.01 (2H,s), 5.45 (1H,d), 6.11 (2H,s), 6.81
 (2H,d), 7.01-7.11 (4H,m), 7.19-7.27 (4H,m), 7.34-7.40
 15 (1H,m); MS: 701 (M+).

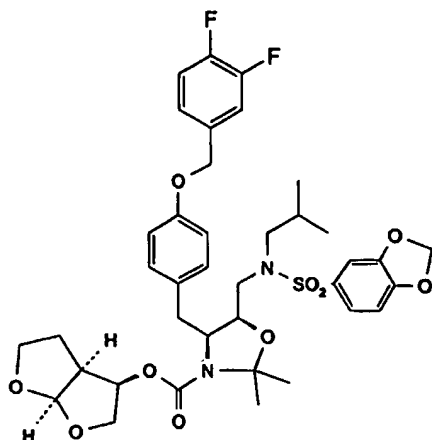
Example 163

20 Step 1:.

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-

-323-

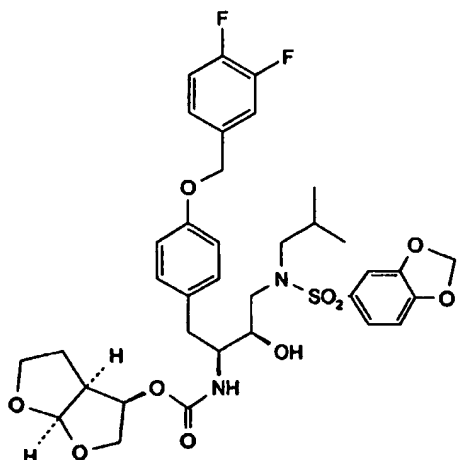
4-{4-[(3,4-difluorobenzyl)oxy]benzyl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate



5 [1]: α -bromo-3,4-difluorotoluene; [2]: 20°C; [3]: 12 hour; MS: 759 (M+).

Step 2:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 10 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-{4-
 [(3,4-difluorobenzyl)oxy]benzyl}-2-hydroxypropylcarbamate
 (379)



[1]: c, Et₂O; [2: 65 %.

-324-

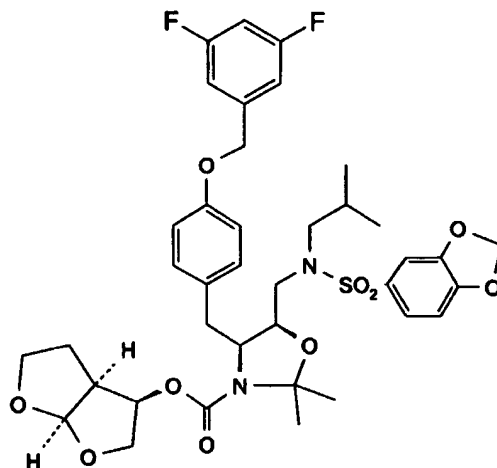
¹H NMR (DMSO-d₆): δ 0.74 (3H,d), 0.80 (3H,d), 1.17 (1H,m),
 1.27-1.32 (1H,m), 1.88-1.92 (1H,m), 2.33 (1H,t), 2.64-
 2.73 (3H,m), 2.88-2.99 (2H,m), 3.42-3.46 (1H,m), 3.53
 5 (3H,m), 3.63 (1H,m), 3.78 (1H,dd), 4.80 (1H,dd), 4.97
 (3H, s(broad)), 5.45 (1H,d), 6.11 (2H,s), 6.80 (2H,d),
 7.00-7.07 (3H,m), 7.19-7.27 (3H,m), 7.35-7.46 (2H,m); MS:
 719 (M+).

10

Example 164

Step 1:

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (4S,5R)-5-
 15 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 4-{4-[(3,5-difluorobenzyl)oxy]benzyl}-2,2-dimethyl-1,3-
 oxazolidine-3-carboxylate



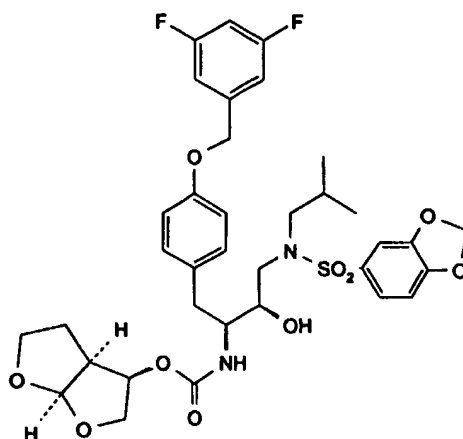
20 [1]: 3,5-difluorobenzylbromide; [2]: 20°C; [3]: 12 hour;
 MS: 759 (M+).

Step 2:

-325-

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-{4-
 [(3,5-difluorobenzyl)oxy]benzyl}-2-hydroxypropylcarbamate
 (380)

5



[1]: c, Et₂O; [2]: 40 %.

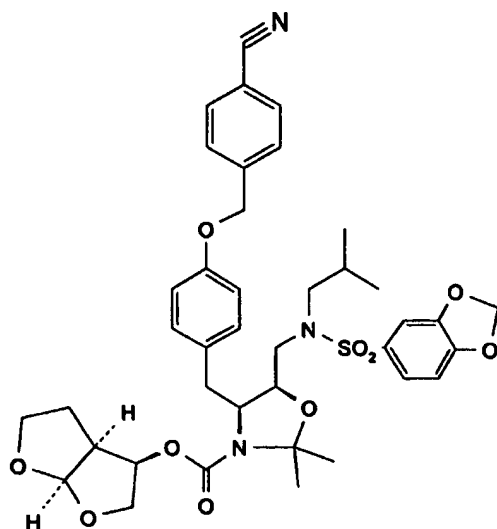
10 ¹H NMR (DMSO-*d*₆): δ 0.74 (3H,d), 0.80 (3H,d), 1.16-1.19
 (1H,m), 1.30 (1H,m), 1.89-1.92 (1H,m), 2.34 (1H,t), 2.64-
 2.73 (3H,m), 2.88-2.99 (2H,m), 3.42-3.46 (1H,m), 3.51-
 3.58 (3H,m), 3.64 (1H,m), 3.79 (1H,dd), 4.80 (1H,dd),
 4.98 (1H,d) 5.03 (2H,s), 5.45 (1H,d), 6.11 (2H,s), 6.81
 15 (2H,d), 7.01-7.15 (6H,m), 7.19-7.27 (2H,m); MS: 719(M⁺).

Example 165

Step 1:

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (4S,5R)-5-
 20 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 4-{4-[(4-cyanobenzyl)oxy]benzyl}-2,2-dimethyl-1,3-
 oxazolidine-3-carboxylate

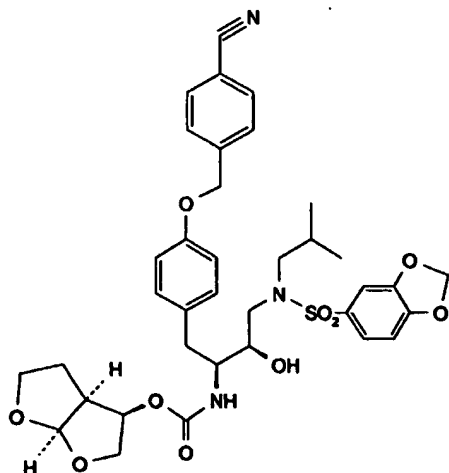
-326-



5 [1]: p-cyanobenzylbromide; [2]: 20°C; [3]: 12 hour; MS:
748 (M⁺) .

Step 2:

(3*R*,3*aS*,6*aR*) -hexahydrofuro[2,3-*b*] furan-3-yl (1*S*,2*R*) -3-
10 [(1,3-benzodioxol-5-ylsulfonyl) (isobutyl) amino] -1-{4-[(4-
cyanobenzyl)oxy]benzyl}-2-hydroxypropylcarbamate (381)



-327-

[1]: b, Hexane-EtOAc (1:3); [2] : 47 %.

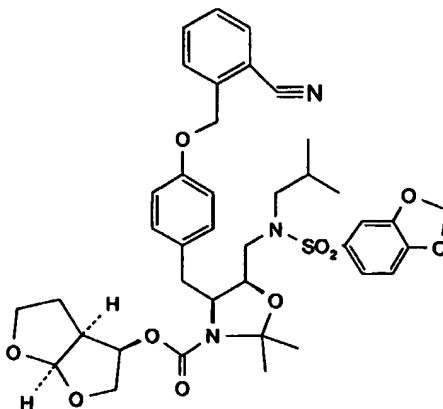
^1H NMR ($\text{DMSO}-d_6$): δ 0.75 (3H,d), 0.81 (3H,d), 1.13-1.30 (2H,m), 1.87-1.94 (1H,m), 2.34 (1H,m), 2.62-2.73 (3H,m), 2.89-3.00 (2H,m), 3.43-3.48 (1H,m), 3.51-3.57 (3H,m), 3.61-3.64 (1H,m), 3.79 (1H,dd), 4.80 (1H,dd), 4.99 (1H,d) 5.11 (2H,s), 5.45 (1H,d), 6.12 (2H,s), 6.82 (2H,d), 7.01-7.08 (3H,m), 7.19-7.28 (2H,m), 7.52 (2H,d), 7.81 (2H,d); MS: 708 (M+).

10

Example 166

Step 1:

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (4S,5R)-5-
{[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
4-{4-[(2-cyanobenzyl)oxy]benzyl}-2,2-dimethyl-1,3-
15 oxazolidine-3-carboxylate

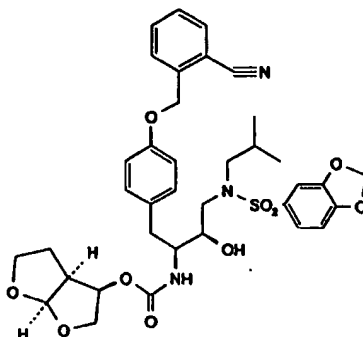


[1]: o-cyanobenzylbromide; [2]: 20°C; [3]: 12 hour; MS:
20 748 (M+).

Step 2:

-328-

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-{4-[(2-
 cyanobenzyl)oxy]benzyl}-2-hydroxypropylcarbamate (382)



5

[1]: b, Hexane-EtOAc (1:3); [2] :47 %.

¹H-NMR (DMSO-*d*₆): δ 0.75 (3H,d), 0.81 (3H,d), 1.19 (1H,m),
 1.31-1.37 (1H,m), 1.91 (1H,m), 2.35 (1H,t), 2.65-2.74
 (3H,m), 2.90-3.00 (2H,m), 3.44-3.49 (1H,m), 3.54 (3H,m),
 10 3.66-3.70 (1H,m), 3.79 (1H,dd), 4.81 (1H,dd), 5.00
 (1H,d), 5.12 (2H,s), 5.45 (1H,d), 6.12 (2H,s), 6.85
 (2H,d), 7.01-7.28 (5H,m), 7.51 (1H,m), 7.62-7.71 (2H,m),
 7.85 (1H,d); MS: 708 (M⁺).

15

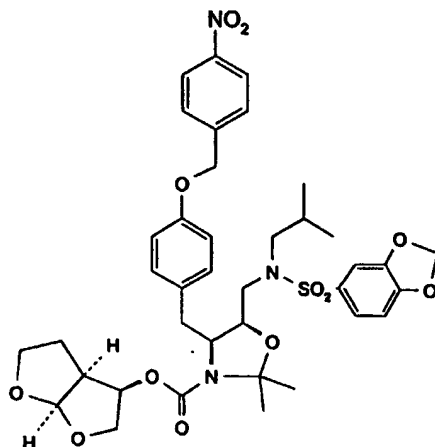
Example 167

Step 1:

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (4S,5R)-5-
 20 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 2,2-dimethyl-4-{4-[(4-nitrobenzyl)oxy]benzyl}-1,3-
 oxazolidine-3-carboxylate

25

-329-



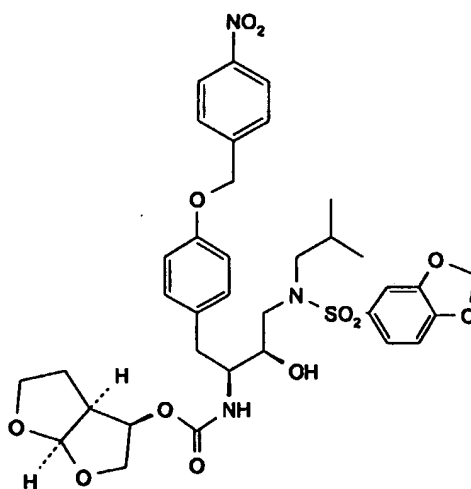
[1]: 4-nitrobenzylbromide; [2]: 20°C; [3]: 3 hour; MS: 768 (M+).

5

Step 2:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-{4-[(4-nitrobenzyl)oxy]benzyl}propylcarbamate (383)

10



[1]: b, Hexane-EtOAc (1:2); [2]: 50 %.

-330-

¹H NMR (DMSO-d₆): δ 0.79 (3H,d), 0.85 (3H,d), 1.24-1.34 (1H,m), 1.95 (1H,m), 2.39 (1H,t), 2.75 (3H,m), 2.93-3.05 (2H,m), 3.34 (1H,m), 3.50-3.68 (5H,m), 3.83 (1H,dd), 4.83 (1H,dd), 5.02 (1H,d), 5.22 (2H,s), 5.48 (1H,d), 6.16 (2H,s), 6.88 (2H,d), 7.05-7.13 (3H,m), 7.24 (2H,m), 7.31 (1H,d), 7.70 (2H,d), 8.24 (2H,d); MS: 728 (M+).

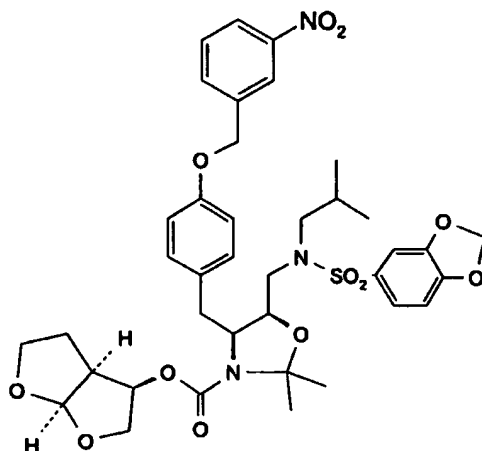
Example 168

Step 1:

10

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
{[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
2,2-dimethyl-4-{4-[(3-nitrobenzyl)oxy]benzyl}-1,3-
oxazolidine-3-carboxylate

15



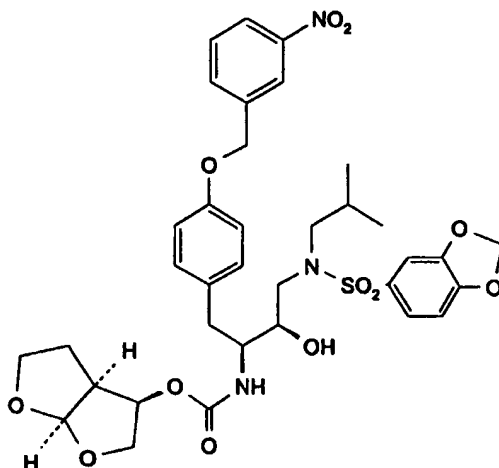
[1]: 3-nitrobenzylbromide; [2]: 20°C; [3]: 3 hour; MS: 768 (M+).

20

Step 2:

-331-

(3*R*, 3*aS*, 6*aR*) -hexahydrofuro[2,3-*b*]furan-3-yl (1*S*, 2*R*) -3-
 [(1,3-benzodioxol-5-ylsulfonyl) (isobutyl) amino] -2-hydroxy
 -1-{4-[(3-nitrobenzyl)oxy]benzyl}propylcarbamate (384)



5

[1]: b, Hexane-EtOAc (1:2); [2]: 44 %.

¹H-NMR (DMSO-*d*₆): δ 0.75 (3H,d), 0.81 (3H,d), 1.12-1.17
 (1H,m), 1.24-1.30 (1H,m), 1.80-1.94 (1H,m), 2.34 (1H,t),
 2.65-2.74 (3H,m), 2.89-3.00 (2H,m), 3.26 (1H,m), 3.43-3.48
 10 (1H,m), 3.51-3.57 (3H,m), 3.61-3.64 (1H,m), 3.79 (1H,dd),
 4.80 (1H,dd), 4.99 (1H,d), 5.17 (2H,s), 5.44 (1H,d), 6.12
 (2H,s), 6.85 (2H,d), 7.02 (1H,d), 7.08 (2H,d), 7.20-7.22
 (2H,m), 7.26 (1H,dd), 7.64 (1H,t), 7.85 (1H,d), 8.14
 (1H,dd), 8.25 (1H,s); MS: 728 (M⁺).

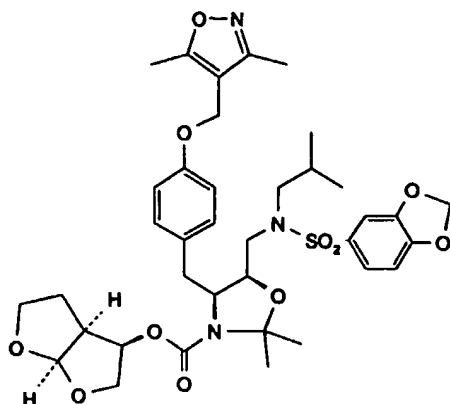
15

Example 169

Step 1:

(3*R*, 3*aS*, 6*aR*) -hexahydrofuro[2,3-*b*]furan-3-yl (4*S*, 5*R*) -5-
 20 {[(1,3-benzodioxol-5-ylsulfonyl) (isobutyl) amino]methyl}-
 4-{4-[(3,5-dimethyl-4-isoxazolyl)methoxy]benzyl}-2,2-
 dimethyl-1,3-oxazolidine-3-carboxylate

- 332 -

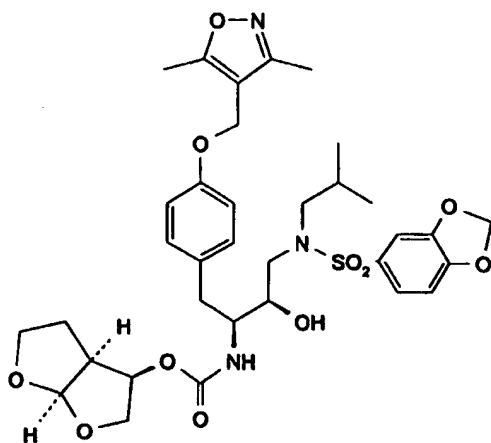


[1]: 4-(chloromethyl)-3,5-dimethylisoxazole; [2]: 20°C;
 [3]: 12 hour; MS: 742 (M+).

5

Step 2:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-{4-
 10 [(3,5-dimethyl-4-isoxazolyl)methoxy]benzyl}-2-
 hydroxypropylcarbamate (385)



15

-333-

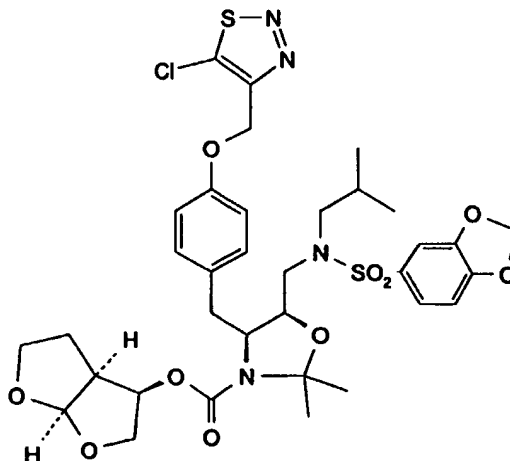
[1]: b, Hexane-EtOAc (1:3); [2] : 49 %.

$^1\text{H-NMR}$ ($\text{DMSO}-d_6$): δ 0.75 (3H,d), 0.81 (3H,d), 1.19 (1H,m),
 1.34 (1H,m), 1.94 (1H,m), 2.14 (3H,s), 2.32 (3H,s), 2.65-
 2.74 (3H,m), 2.93 (2H,m), 3.44 (1H,m), 3.52-3.57 (3H,m),
 5 3.69 (1H,m), 3.78-3.82 (1H,m), 4.78-4.83 (3H,m), 4.99-
 5.00 (1H,m), 5.48 (1H,m), 6.12 (2H,s), 6.81 (2H,d), 7.03
 (1H,d), 7.07 (2H,d), 7.20-7.28 (3H,m); MS: 702 (M^+).

Example 170

10 Step 1:

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (4S,5R)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 4-{4-[(5-chloro-1,2,3-thiadiazol-4-yl)methoxy]benzyl}-
 15 2,2-dimethyl-1,3-oxazolidine-3-carboxylate



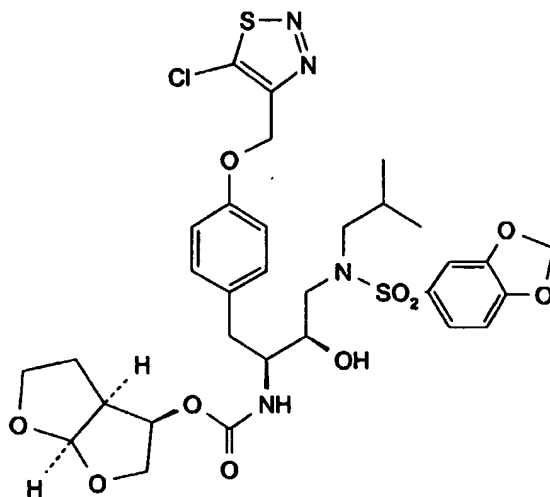
[1]: 5-chloro-4-(chloromethyl)1,2,3-thiadiazole; [2]:
 20 20°C; [3]: 12 hour; MS: 765 (M^+).

Step 2:

-334-

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-{4-[(5-
 chloro-1,2,3-thiadiazol-4-yl)methoxy]benzyl}-2-
 hydroxypropylcarbamate (386)

5



[1]: b, Hexane-EtOAc (1:3); [2] : 38 %.

¹H NMR (DMSO-*d*₆): δ 0.75 (3H,d), 0.81 (3H,d), 1.19 (1H,m),
 1.32 (1H,m), 1.94 (1H,m), 2.35 (1H,m), 2.67-2.74 (3H,m),
 10 2.91-3.01 (2H,m), 3.46(1H,m), 3.52-3.56 (3H,m), 3.66-3.70
 (1H,m), 3.80 (1H,dd), 4.81 (1H,dd), 5.00 (1H,d), 5.35
 (2H,s), 5.46 (1H,d), 6.12 (2H,s), 6.90 (2H,d), 7.03
 (1H,d), 7.10 (2H,d), 7.20-7.22 (2H,m), 7.26-7.31 (1H,m);
 MS: 725(M⁺).

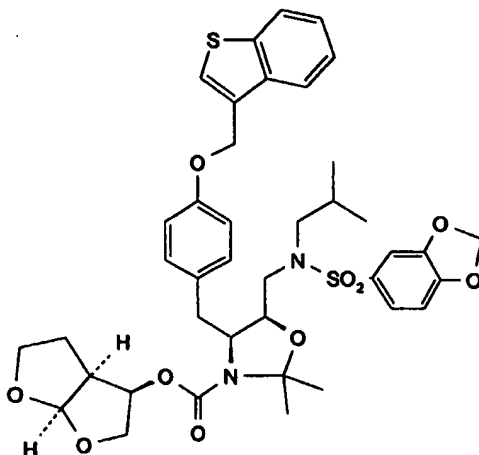
15

Example 171

Step 1:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
 20 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 4-[4-(1-benzothien-3-ylmethoxy)benzyl]-2,2-dimethyl-1,3-
 oxazolidine-3-carboxylate

-335-



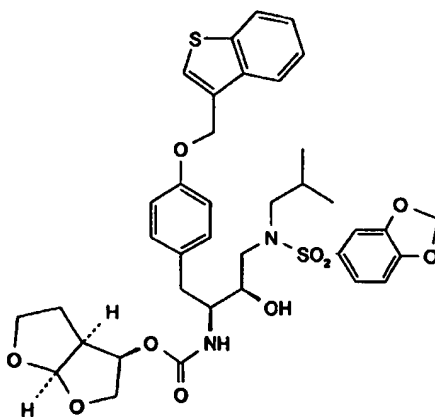
[1]: 3-(chloromethyl)-1-benzothiophene; [2]: 20°C; [3]: 12 hour.

5

Step 2:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-(1-benzothien-3-ylmethoxy)benzyl]-2-hydroxypropylcarbamate

10 (387)



[1]: b, Hexane-EtOAc (1:3); [2]): 8.9 %.

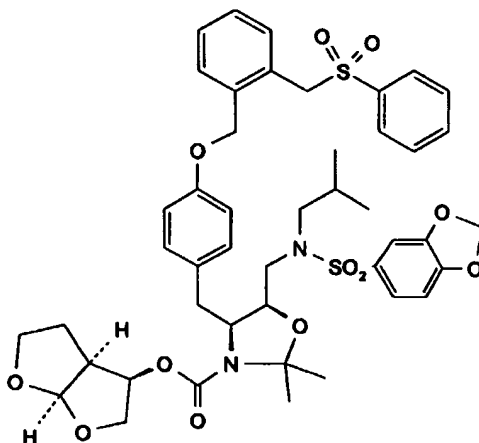
-336-

^1H NMR ($\text{DMSO}-d_6$): δ 0.75 (3H,d), 0.81 (3H,d), 1.15-1.19 (1H,m), 1.30 (1H,m), 1.90-1.93 (1H,m), 2.35 (1H,t), 2.65-2.74 (3H,m), 2.90-3.00 (2H,m), 3.27 (1H,m), 3.44-3.49 (1H,m), 3.52-3.58 (3H,m), 3.63-3.67 (1H,m), 3.80 (1H,dd), 4.81 (1H,dd), 5.00 (1H,d), 5.24 (2H,s), 5.45 (1H,d), 6.12 (2H,s), 6.89 (2H,d), 7.02 (1H,d), 7.08 (2H,d), 7.20-7.22 (2H,m), 7.26-7.28 (1H,m), 7.33-7.39 (2H,m), 7.80-7.83 (2H,m), 7.95-7.97 (1H,m); MS: 739 (M^+).

10

Example 172

Step 1:



(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (4S,5R)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 2,2-dimethyl-4-[4-[(2-[(phenylsulfonyl)methyl]benzyl]
 15 oxy)benzyl]-1,3-oxazolidine-3-carboxylate

[1]: 1-(bromomethyl)-2-[(phenylsulfonyl)methyl]benzene;

[2]: 20°C; [3]: 12 hour.

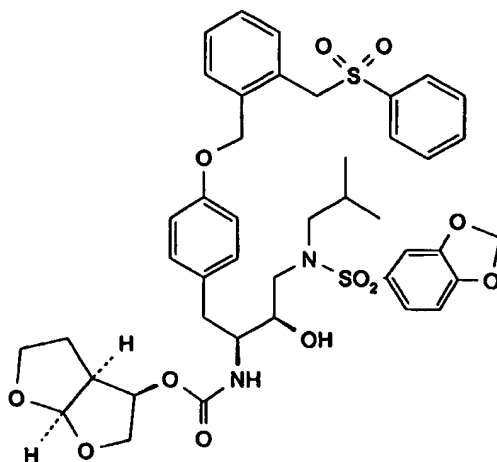
20

Step 2:

-337-

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-[4-({2-[(phenylsulfonyl)methyl]benzyl}oxy)
 benzyl]propylcarbamate (388)

5



[1]: b, Hexane-EtOAc (1:1); [2] :16 %.

¹H NMR (DMSO-*d*₆): δ 0.75 (3H,d), 0.81 (3H,d), 1.19 (1H,m),
 1.31 (1H,m), 1.90-1.94 (1H,m), 2.35 (1H,t), 2.61-2.74
 10 (3H,m), 2.90-3.01 (2H,m), 3.46 (1H,m), 3.52-3.56 (3H,m),
 3.66 (1H,m), 3.79 (1H,dd), 4.75 (2H,s), 4.79-4.84 (1H,m),
 4.99-5.02 (3H,m), 5.45 (1H,d), 6.12 (2H,s), 6.79 (2H,d),
 7.01-7.08 (4H,m), 7.02 (2H,m), 7.23-7.32 (3H,m), 7.40
 (1H,d), 7.54-7.61 (2H,m), 7.68-7.76 (3H,m); MS: 837(M⁺).

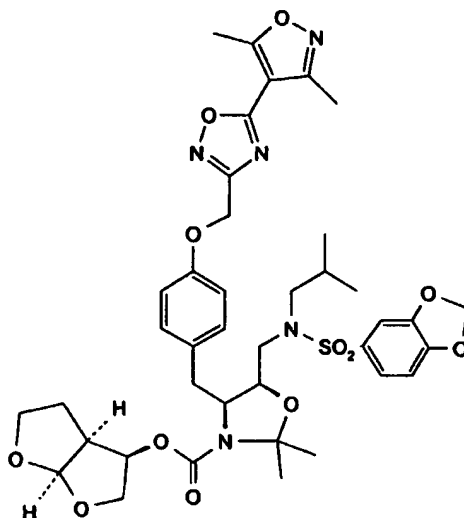
15

Example 173

Step 1:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 20 4-(4-{[5-(3,5-dimethyl-4-isoxazolyl)-1,2,4-oxadiazol-3-
 yl]methoxy}benzyl)-2,2-dimethyl-1,3-oxazolidine-3-
 carboxylate

-338-

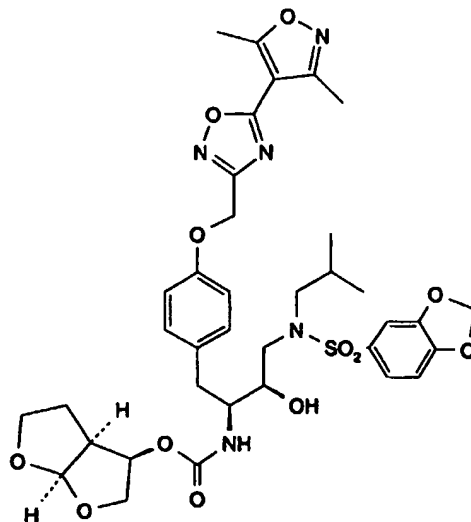


[1]: 3-(chloromethyl)-5-(3,5-dimethyl-4-isoxazolyl)-
 5 1,2,4-oxadiazole; [2]: 20°C; [3]: 1 hour.

Step 2:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-(4-{[5-
 10 (3,5-dimethyl-4-isoxazolyl)-1,2,4-oxadiazol-3-
 yl]methoxy}benzyl)-2-hydroxypropylcarbamate (389)

[1]: b, Hexane-EtOAc (1:3); [2]: 4 %.



-339-

¹H NMR (DMSO-*d*₆): δ 0.74 (3H,d), 0.81 (3H,d), 1.13-1.28 (2H,m), 1.90 (1H,m), 2.31-2.37 (2H,m), 2.71 (6H,m), 2.90-3.00 (2H,m), 3.46-3.53 (4H,m), 3.64 (1H,m), 3.78 (1H,m), 4.80 (1H,m), 5.01 (1H,m), 5.23 (2H,m), 6.11 (2H,s), 6.88 (2H,d), 7.02 (1H,dd), 7.09 (1H,d), 7.19-7.22 (2H,m), 7.26 (1H,d); MS: 770 (M⁺).

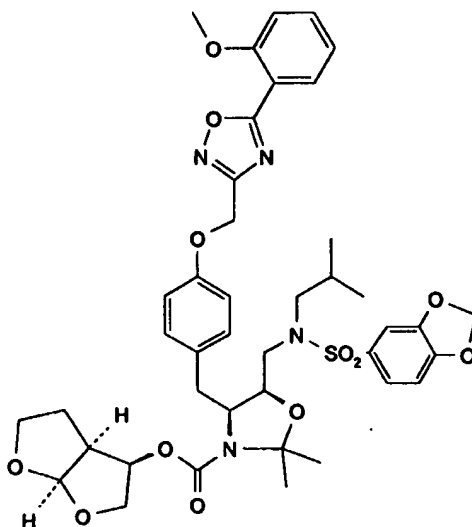
Example 174

Step 1:

10

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 4-(4-{[5-(2-methoxyphenyl)-1,2,4-oxadiazol-3-
 yl]methoxy}benzyl)-2,2-dimethyl-1,3-oxazolidine-3-

15 carboxylate



[1]: 3-(chloromethyl)-5-(2-methoxyphenyl)-1,2,4-oxadiazole; [2]: 20°C; [3]: 1 hour.

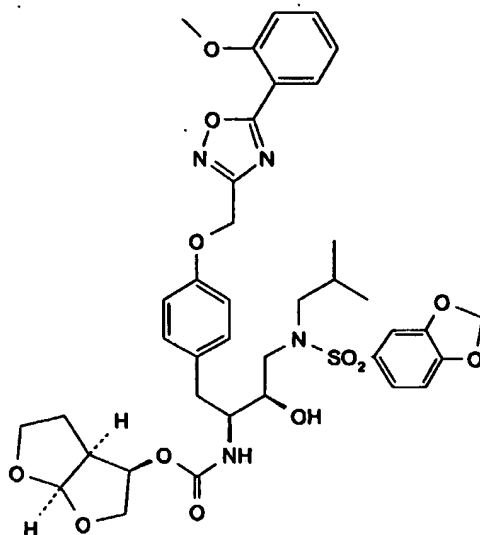
20

Step 2:

-340-

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-
 hydroxy-1-(4-{[5-(2-methoxyphenyl)-1,2,4-oxadiazol-3-
 yl]methoxy}benzyl)propylcarbamate (390)

5



[1]: b, Hexane-EtOAc (1:2); [2]:24 %.

¹H NMR (DMSO-*d*₆): δ 0.75 (3H,d), 0.81 (3H,d), 1.12-1.19
 10 (1H,m), 1.26-1.37 (1H,m), 1.90-1.93 (1H,m), 2.28-2.38
 (1H,m), 2.62-2.74 (3H,m), 2.90-3.00 (2H,m), 3.45(1H,m),
 3.51-3.55 (3H,m), 3.64-3.69 (1H,m), 3.78 (1H,dd), 3.88
 (3H,s), 4.79 (1H,dd), 5.00 (1H,d), 5.22 (2H,s), 5.40
 (1H,d), 6.12 (2H,s), 6.88 (2H,d), 7.02 (1H,d), 7.08-7.12
 15 (3H,m), 7.20-7.23 (2H,m), 7.26 (2H,d), 7.63 (1H,t), 7.94
 (1H,d); MS: 781 (M⁺).

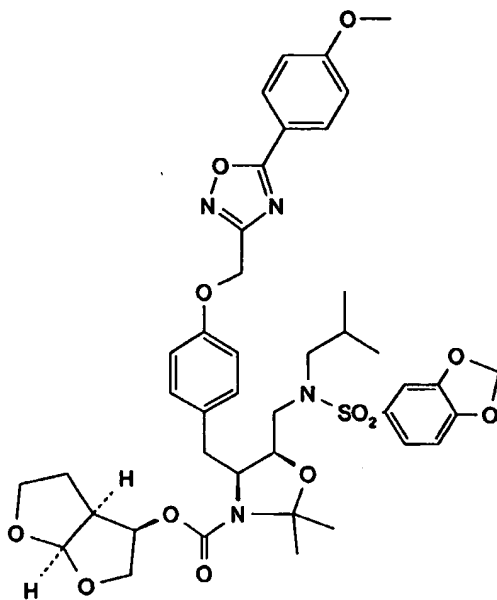
Example 175

20 Step 1:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-

-341-

4-(4-{[5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl]methoxy}benzyl)-2,2-dimethyl-1,3-oxazolidine-3-carboxylate



5

[1]: 3-(chloromethyl)-5-(4-methoxyphenyl)-1,2,4-oxadiazole; [2]: 20°C; [3]: 1 hour.

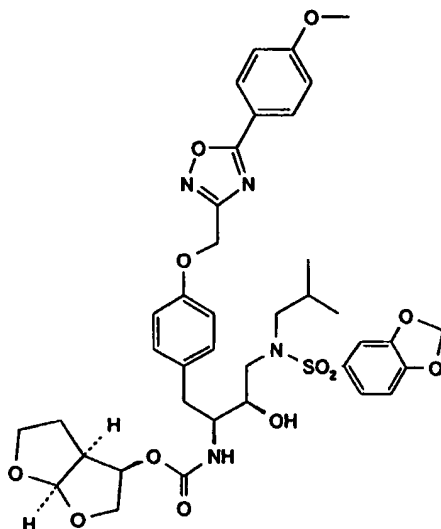
10 Step 2:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-(4-{[5-(4-methoxyphenyl)-1,2,4-oxadiazol-3-yl]methoxy}benzyl)propylcarbamate (391)

15

20

-342-



5

[1]: a, Hexane-EtOAc (1:5); [2] : 44 %.

^1H NMR ($\text{DMSO}-d_6$): δ 0.75 (3H,d), 0.81 (3H,d), 1.12-1.19 (1H,m), 1.24-1.36 (1H,m), 1.91 (1H,m), 2.32-2.38 (1H,m), 2.62-2.74 (3H,m), 2.90-3.00 (2H,m), 3.46 (1H,m), 3.51-3.55 (3H,m), 3.66 (1H,m), 3.76-3.79 (1H,m), 3.82 (3H,m), 4.79 (1H,dd), 5.00 (1H,d), 5.20 (2H,s), 5.40 (1H,d), 6.12 (2H,s), 6.88 (2H,d), 7.02 (1H,d), 7.08-7.13 (3H,m), 7.20-7.23 (2H,m), 7.26 (1H,d), 8.02 (2H,d); MS: 781 (M+).

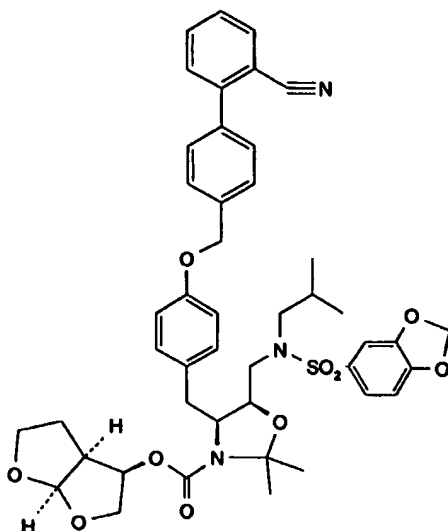
15

Example 176

Step 1:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 4-{4-[(2'-cyano[1,1'-biphenyl]-4-yl)methoxy]benzyl}-2,2-
 dimethyl-1,3-oxazolidine-3-carboxylate

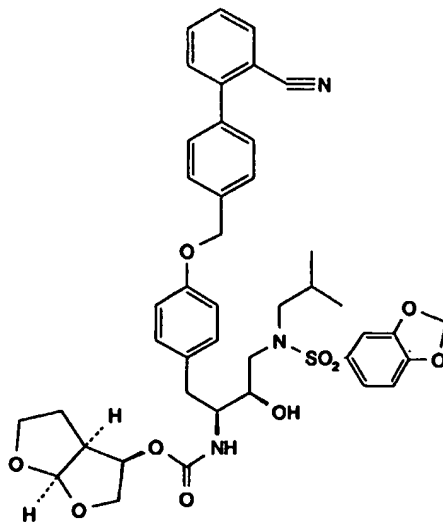
-343-



[1]: 4'-(bromomethyl)[1,1'-biphenyl]-2-carbonitrile; [2]:
 5 20°C; [3]: 3 hour; MS: 824 (M+).

Step 2:

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-{4-
 10 [(2'-cyano[1,1'-biphenyl]-4-yl)methoxy]benzyl}-2-
 hydroxypropylcarbamate (392)



-344-

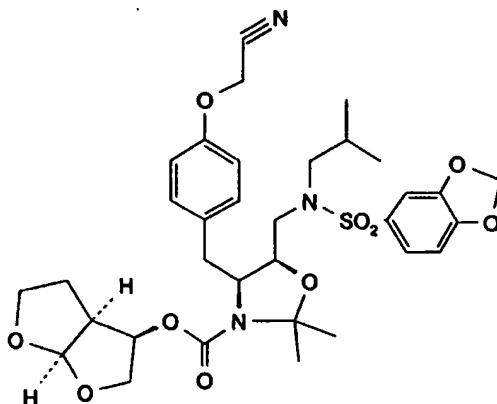
[1]: b, Hexane-EtOAc (1:2); [2] :54 %.

¹H NMR (DMSO-*d*₆): δ 0.75 (3H,d), 0.81 (3H,d), 1.19 (1H,m),
 1.26-1.38 (1H,m), 1.92 (1H,m), 2.32-2.38 (1H,m), 2.65-
 5 2.75 (3H,m), 2.90-3.01 (2H,m), 3.30 (1H,m), 3.46 (1H,m),
 3.52-3.56 (3H,m), 3.66 (1H,m), 3.79 (1H,dd), 4.81
 (1H,dd), 4.99 (1H,d), 5.08 (2H,s), 5.44 (1H,d), 6.12
 (2H,s), 6.86 (2H,d), 7.02 (1H,d), 7.08 (2H,d), 7.20-7.22
 (2H,m), 7.27 (1H,dd), 7.52-7.60 (6H,m), 7.75 (1H,t), 7.91
 10 (1H,d); MS: 784 (M⁺).

Example 177

Step 1:

15 (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 4-[4-(cyanomethoxy)benzyl]-2,2-dimethyl-1,3-oxazolidine-
 3-carboxylate



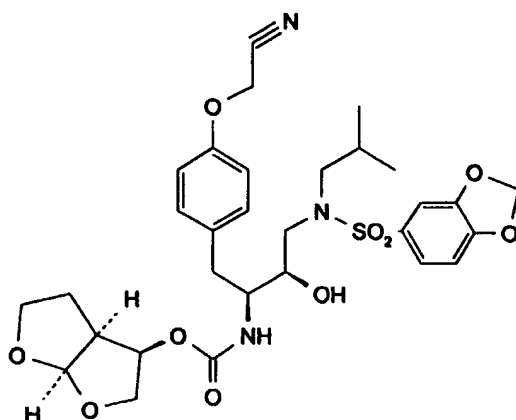
20

[1]: chloroacetonitrile; [2]: 20°C; [3]: 3 hour; MS: 672
 (M⁺).

Step 2:

-345-

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-1-[4-
 (cyanomethoxy)benzyl]-2-hydroxypropylcarbamate (393)



5

[1]: c, Hexane-EtOAc (50:1); [2] : 48 %.

¹H NMR (DMSO-*d*₆): δ 0.75 (3H,d), 0.81 (3H,d), 1.20 (1H,m),
 1.36-1.41 (1H,m), 1.91 (1H,m), 2.31-2.37 (1H,m), 2.65-
 10 2.74 (3H,m), 2.89-3.00 (2H,m), 3.43 (1H,m), 3.52-3.60
 (2H,m), 3.71 (1H,m), 3.78-3.82 (1H,m), 4.29-4.34 (2H,m),
 4.79-4.84 (1H,m), 5.00 (1H,d), 5.46 (1H,d), 6.12 (2H,s),
 6.76 (2H,d), 7.01-7.07 (3H,m), 7.20-7.28 (1H,m), 7.26
 (1H,m), 7.33 (1H,m), 7.45 (1H,m); MS: 632 (M+).

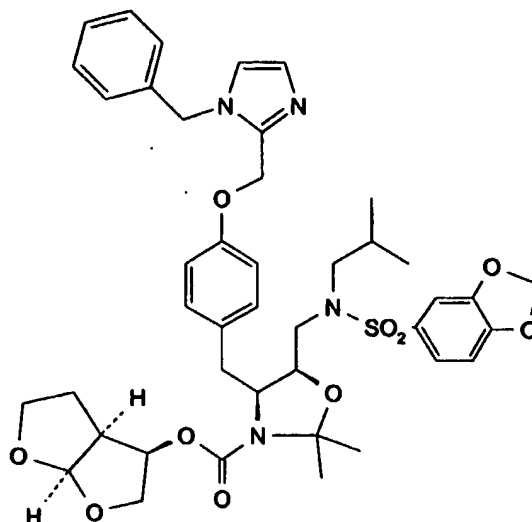
15

Example 178

Step 1:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
 20 {[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]methyl}-
 4-{4-[(1-benzyl-1*H*-imidazol-2-yl)methoxy]benzyl}-2,2-
 dimethyl-1,3-oxazolidine-3-carboxylate

-346-

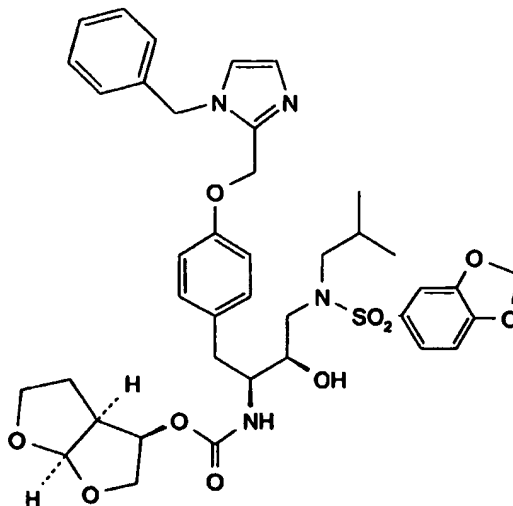


[1]: 1-benzyl-2-(chloromethyl)-1H-imidazole

5 hydrochloride; [2]: 20°C; [3]: 3 hour; MS: 803 (M+).

Step 2:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)isobutyl]amino]-1-{4-[(1-
 10 benzyl-1*H*-imidazol-2-yl)methoxy]benzyl}-2-
 hydroxypropylcarbamate (394)



-347-

[1]: b, EtOAc-EtOH(1:1); [2] : 29 %.

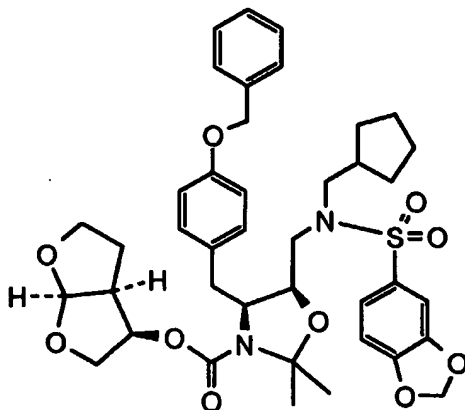
¹H-NMR (DMSO-*d*₆): δ 0.75 (3H,d), 0.81 (3H,d), 1.11-1.32 (2H,m), 1.88-1.94 (1H,m), 2.28-2.40 (1H,m), 2.65-2.74 (3H,m), 2.86-3.01 (2H,m), 3.26(1H,m), 3.43-3.48 (1H,m), 3.52-3.57 (2H,m), 3.62-3.66 (1H,m), 3.79 (1H,dd), 4.81 (1H,dd), 4.95-5.05 (3H,m), 5.19 (2H,s), 5.45 (1H,d), 6.12 (2H,s), 6.80 (2H,d), 6.88 (1H,m), 7.02-7.06 (3H,m), 7.11-7.15 (2H,m), 7.20-7.30 (6H,m); MS: 763(M⁺).

10

Example 179

Step 1:

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (4S,5R)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(cyclopentylmethyl)
 amino]methyl}-4-[4-(benzyloxy)benzyl]-2,2-dimethyl-1,3-
 15 oxazolidine-3-carboxylate



The reaction was carried out as described for N-(3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-oxycarbonyl-, (4S,5R)-4-(4-benzyloxy-benzyl)-5-i-butyl-[(3,4-methylenedioxyphenyl)sulfonyl]-aminomethyl-2,2-dimethyl-oxazolidine. (Y=67%)

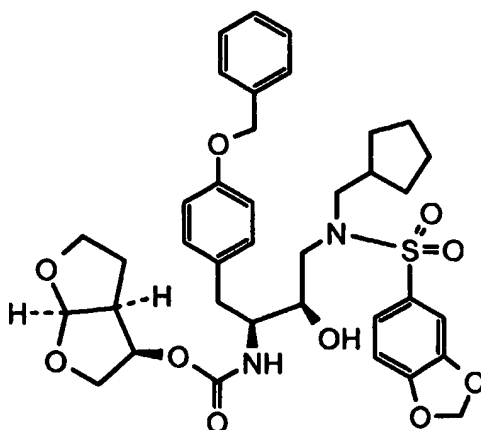
20

-348-

^1H NMR (CDCl_3): δ 1.08 (1H,m), 1.25 (2H,m), 1.45-1.80 (5H,m), 1.48 (3H,s), 1.64 (3H,s), 1.85 (2H,m), 2.25 (1H,m), 2.65-3.45 (7H,m), 3.80 (3H,m), 3.95 (1H,m), 4.21 (1H,m), 4.28 (1H,m), 4.88 (1H,dd), 5.03 (2H, s), 5.65 (1H,d), 6.01 (2H,s), 6.80-7.50 (12H,m).

Step 2:

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-
 10 [(1,3-benzodioxol-5-ylsulfonyl) (cyclopentylmethyl) amino] -
 1-[4-(benzyloxy)benzyl]-2-hydroxypropylcarbamate (395)



15 The carbamate formation was carried out as described for
 (3R,3aS,6aR)-Hexahydrofuro[2,3-b]furan-3-yl-N((1S,2R)-1-
 (4-benzyloxy-benzyl)-3-i-butyl-[(3,4-
 methylenedioxyphenyl) sulfonyl]-amino-2-hydroxypropyl-
 carbamate. (Y=79%)

20

^1H NMR ($\text{DMSO}-d_6$): δ 1.05 (1H,m), 1.20 (1H,m), 1.30-1.70 (8H,m), 2.19 (1H,m), 2.36 (1H,t), 2.70-2.95 (4H,m), 3.10 (1H,dd), 3.40-3.60 (4H,m), 3.65 (1H,t), 3.80 (1H,dd),

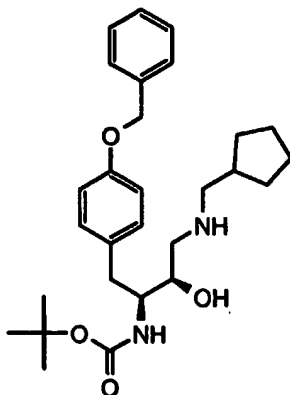
-349-

4.81 (1H,dd), 5.00 (3H, s+d), 5.46 (1H,d), 6.13 (2H,s),
6.83 (2H,d), 7.00-7.41 (11H,m). MS: 708 (M)+.

Example 180

5 Step 1:

**tert-butyl (1*S*,2*R*)-1-[4-(benzyloxy)benzyl]-3-
[(cyclopentylmethyl)amino]-2-hydroxypropylcarbamate**



10

The reaction was carried out as described above except cyclopentylmethylamine was used in the reaction. (Y: 91%)

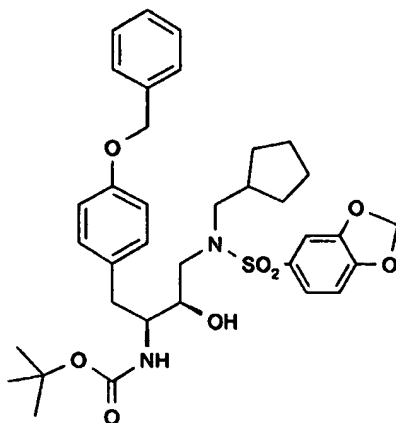
15 ¹H NMR: (CDCl₃): δ 1.08-1.23 (2H,m), 1.34 (9H,s), 1.48-
1.59 (4H,m), 1.72-1.77 (2H,m), 1.91-2.02 (1H,m), 2.45-
2.54 (2H,m), 2.67 (2H,m), 2.77-2.82 (1H,m), 2.88 (1H,dd),
3.41 (1H,m), 3.73 (1H,m), 4.64 (1H,d), 5.01 (2H,s), 6.88
20 (2H,d), 7.12 (2H,d), 7.28-7.41 (4H,m).

20

Step 2:

-350-

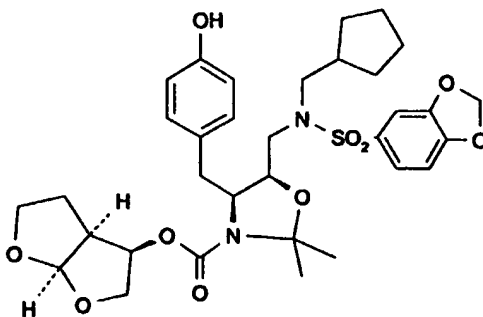
**tert-butyl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)
(cyclopentylmethyl)amino]-1-[4-(benzyloxy)benzyl]-2-
hydroxypropylcarbamate**



- 5 The reaction was carried out as described above except
tert-butyl (1*S*,2*R*)-1-[4-(benzyloxy)benzyl]-3-
[(cyclopentylmethyl)amino]-2-hydroxypropylcarbamate was
used in the reaction. (Y: 88%)
This compound was used as is in the next step without
10 additional purification.

Step 3:

- (3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
{[(1,3-benzodioxol-5-ylsulfonyl)(cyclopentylmethyl)
15 amino]methyl}-4-(4-hydroxybenzyl)-2,2-dimethyl-1,3-
oxazolidine-3-carboxylate



-351-

This reaction was carried out as described above except
tert-butyl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-
ylsulfonyl)(cyclopentylmethyl)amino]-1-[4-
(benzyloxy)benzyl]-2-hydroxypropylcarbamate was used in
5 the reaction. (Y: 59%)

¹H NMR: (CDCl₃): δ 1.02-1.12 (1H,m), 1.20-1.33 (1H,m),
1.45-1.76 (5H,m), 1.47 (3H,s), 1.65 (3H,s), 1.87 (2H,m),
2.16-2.30 (1H,m), 2.66-2.70 (2H,m), 2.78-2.88 (2H,m),
10 2.98-3.04 (1H,m), 3.11-3.20 (1H,m), 3.37-3.41 (2H,m),
3.75-3.85 (2H,m), 3.91-3.96 (1H,m), 4.17-4.21 (1H,m),
4.26-4.28 (1H,m), 4.87 (1H,dd), 5.66 (1H,dd), 6.04
(2H,s), 6.74 (2H,d), 6.82 (1H,d), 6.96 (2H,d), 7.02
(1H,d), 7.04-7.07 (1H,m), 7.11 (1H,dd)

15

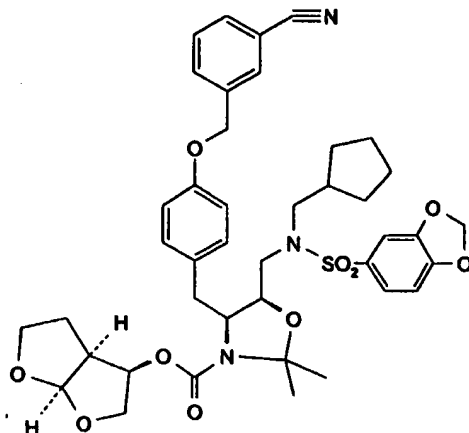
Step 4:

General procedure for the aralkylation of (3*R*,3*aS*,6*aR*)-
hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-{[(1,3-
benzodioxol-5-ylsulfonyl)(cyclopentylmethyl)
20 amino]methyl}-4-(4-hydroxybenzyl)-2,2-dimethyl-1,3-
oxazolidine-3-carboxylate

This procedure was carried out as described before using
aralkyl halide [1], stirring at the indicated temperature
25 [2] for the indicated number of hours [3].

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (4*S*,5*R*)-5-
{[(1,3-benzodioxol-5-ylsulfonyl)(cyclopentylmethyl)
30 amino]methyl}-4-{4-[(3-cyanobenzyl)oxy]benzyl}-2,2-
dimethyl-1,3-oxazolidine-3-carboxylate

- 352 -



[1]: 3-cyanobenzyl bromide; [2]: 20°C; [3]: 12 hour; MS:
 5 774 (M+).

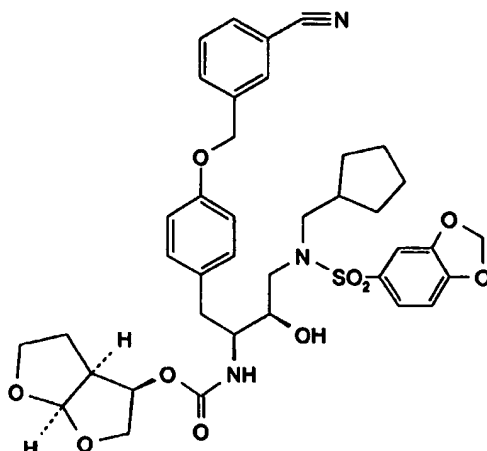
Step 5:

General Procedure for the deprotection

10 This reaction was carried out as before using HCl/dioxane

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(cyclopentylmethyl)amino]-
 1-{4-[(3-cyanobenzyl)oxy]benzyl}-2-hydroxypropylcarbamate
 15 (396)

-353-



[1]: c, EtOAc-Hexane; [2] :60%.

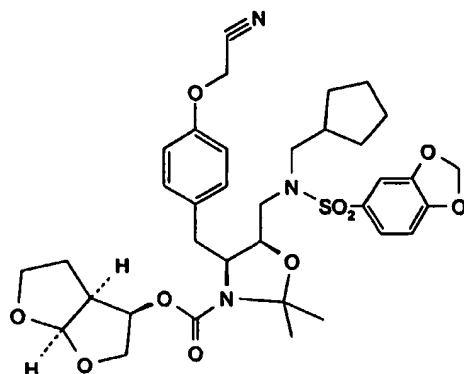
5 1H-NMR: (DMSO): δ 1.10 (1H,m), 1.17-1.32 (2H,m), 1.35-1.72 (5H,m), 2.21 (1H,m), 2.39 (1H,m), 2.74-3.00 (4H,m), 3.11-3.18 (1H,m), 3.46-3.62 (4H,m), 3.64-3.70 (1H,m), 3.84 (1H,dd), 4.85 (1H,dd), 5.03 (1H,m), 5.11 (2H,s), 5.50 (1H,d) 6.16 (2H,s), 6.87 (2H,d), 7.05-7.13 (3H,m),
 10 7.25 (2H,d), 7.31 (1H,d), 7.60 (1H,t), 7.76-7.80 (2H,m), 7.88 (1H,s); MS: 734 (M+).

Example 181

15 Step 1

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (4S,5R)-5-{[(1,3-benzodioxol-5-ylsulfonyl)(cyclopentylmethyl)amino]methyl}-4-[4-(cyanomethoxy)benzyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate

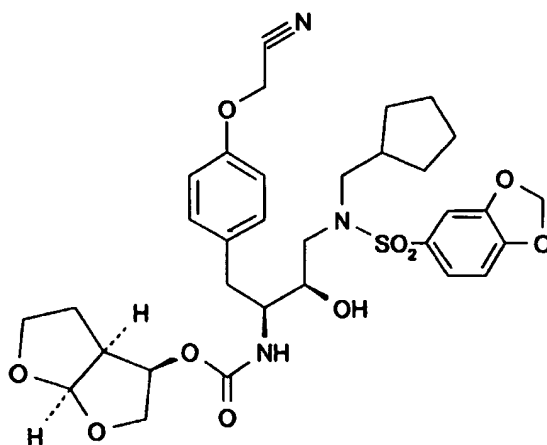
-354-



[1]: chloroacetonitrile; [2]: 20°C; [3]: 12 hour; MS: 698 (M⁺).

5 Step 2:

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-[(1,3-benzodioxol-5-ylsulfonyl)(cyclopentylmethyl)amino]-1-[4-(cyanomethoxy)benzyl]-2-hydroxypropylcarbamate (397)



10

[1]: b, EtOAc-Hexane (2:1); [2] : 77%.

-355-

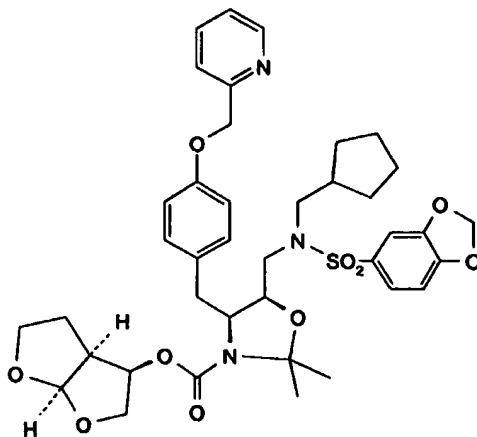
¹H NMR: (DMSO): δ 1.10 (1H,m), 1.24 (2H,m), 1.40-1.70 (7H,m), 2.20-2.26 (1H,m), 2.35-2.43 (1H,m), 2.78-2.98 (4H,m), 3.11-3.19 (1H,m), 3.48-3.51 (1H,m), 3.55-3.65 (3H,m), 3.73-3.78 (1H,m), 3.84 (1H,dd), 4.33 (2H,s), 4.85 (1H,dd), 5.02 (1H,d), 5.51 (1H,d), 6.16 (2H,s), 6.80 (2H,d), 7.05-7.12 (3H,m), 7.22-7.25 (1H,m), 7.31 (1H,dd), 7.36 (1H,m), 7.46 (1H,m); MS: 658 (M+).

10

Example 182

Step 1:

(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (4S,5R)-5-
 {[(1,3-benzodioxol-5-ylsulfonyl)(cyclopentylmethyl)
 15 amino]methyl}-2,2-dimethyl-4-[4-(2-
 pyridinylmethoxy)benzyl]-1,3-oxazolidine-3-carboxylate



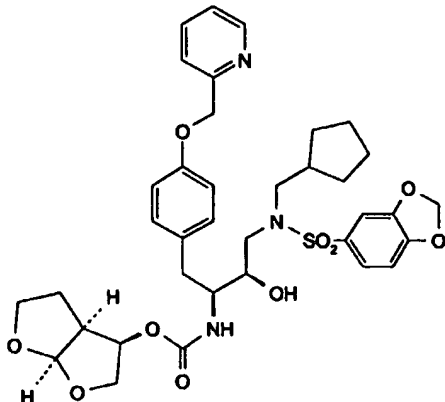
20 [1]: 2-picolylchloride HCl; [2]: 20°C; [3]: 12 hour; MS:
 750 (M+).

Step 2:

-356-

(3*R*,3*aS*,6*aR*)-hexahydrofuro[2,3-*b*]furan-3-yl (1*S*,2*R*)-3-
 [(1,3-benzodioxol-5-ylsulfonyl)(cyclopentylmethyl)amino]-
 2-hydroxy-1-[4-(2-pyridinylmethoxy)benzyl]propylcarbamate
 (398)

5



[1]: b, EtOAc; [2] :47%.

10 ^1H NMR: (DMSO): δ 1.14 (1H,m), 1.24 (2H,m), 1.40-1.70
 (7H,m), 2.22 (1H,m), 2.39 (1H,m), 2.74-2.96 (4H,m), 3.10-
 3.15 (1H,m), 3.51-3.59 (4H,m), 3.63-3.70 (1H,m), 3.83
 (1H,dd), 4.84 (1H,dd), 5.01 (1H,m), 5.10 (2H,s), 5.27
 (1H,d) 6.15 (2H,s), 6.87 (2H,d), 7.04-7.12 (3H,m), 7.21-
 15 7.25 (2H,m), 7.30-7.34 (2H,m), 7.48 (1H,d), 7.81 (1H,t),
 8.55 (1H,d); MS: 710 (M+).

Example 183

Anti-Viral Activity

20 We measured the enzyme inhibition constants of
 the compounds listed in Table I against HIV-1 protease
 using the methods of: B. Maschera et al., "Human
 Immunodeficiency Virus: Mutations in the Viral Protease
 that Confer Resistance to Saquinavir Increase the

-357-

Dissociation Rate Constant for the Protease-Saquinavir Complex", J. Biol. Chem., 271, pp. 33231-35 (1996); and M. V. Toth et al., Int. J. Peptide Protein Res. 36, pp. 544-50 (1990)

5

Antiviral activity assay in MT4 cells

Antiviral HIV activity and compound-induced cytotoxicity were measured in parallel by means of a propidium iodide based procedure in the human T-cell lymphotropic virus transformed cell line MT4. Aliquots of the test compounds were serially diluted in medium (RPMI 1640, 10% fetal calf serum (FCS), and gentamycin) in 96-well plates (Costar 3598) using a Cetus Pro/Pette. Exponentially growing MT4 cells were harvested and centrifuged at 1000 rpm for 10 min in a Jouan centrifuge (model CR 4 12). Cell pellets were resuspended in fresh medium (RPMI 1640, 20% FCS, 20% IL-2, and gentamycin) to a density of 5×10^5 cells/ml. Cell aliquots were infected by the addition of HIV-1 (strain IIIB) diluted to give a viral multiplicity of infection of 100 x TCID₅₀. A similar cell aliquot was diluted with medium to provide a mock-infected control. Cell infection was allowed to proceed for 1 hr at 37° in a tissue culture incubator with humidified 5% CO₂ atmosphere. After the 1 hr incubation the virus/cell suspensions were diluted 6-fold with fresh medium, and 125 µl of the cell suspension was added to each well of the plate containing pre-diluted compound. Plates were then placed in a tissue culture incubator with humidified 5% CO₂ for 5 days. At the end of the incubation period, 27 µl of 5% Nonidet-40 was added to each well of the incubation plate. After thorough mixing with a Costar multitip pipetter, 60 µl of

-358-

the mixture was transferred to filter-bottomed 96-well plates. The plates were analyzed in an automated assay instrument (Screen Machine, Idexx Laboratories). The assay makes use of a propidium iodide dye to estimate the DNA content of each well.

REFERENCES

1. Averett, D.R. 1989. Anti-HIV compound assessment by two novel high capacity assays. *J. Virol. Methods* 23: 263-276.
2. Schwartz, O., et al. 1988. A rapid and simple colorimetric test for the study of anti-HIV agents. *AIDS Res. and Human Retroviruses*, 4(6):441-447.
3. Daluge, S.M., et al. 1994. 5-chloro-2'3'-deoxy-3'fluorouridine (935U83), a selective anti-human immuno-deficiency virus agent with an improved metabolic and toxicological profile. *Antimicro. Agents and Chemother.*, 38 (7):1590-1603.

The anti-viral potency in MT-4 cells of the compounds set forth in Tables 1 and 2 was determined using the above technique. The results are shown in Table A.

Table A. Antiviral Activity of Compounds of the Invention.

Cmpd #	IC ₅₀	Cmpd #	IC ₅₀	Cmpd #	IC ₅₀
5a	NA	26	A	48	B
5b	NA	27	D	49	B
5c	NA	28	E	50	C

-359-

5d	NA	29	C	51	B
5e	NA	30	C	52	B
5f	NA	31	B	53	B
5g	NA	32	C	54	B
6e	NA	33	C	55	A
10	D	34	D	56	C
11	D	35	C	57	B
12	E	36	C	58	E
13	D	37	C	59	NA
14	NA	38	A	60	NA
15	D	39	NA	61	NA
16	D	40	NA	67	D
17	D	41	NA	68	D
18	C	42	D	69	D
19	E	43	C	70	D
20	C	44	A	71	B
21	C	46	A	72	B
22	C	47	NA	73	C
23	C			74	D
24	C				
25	C				

In Table A, the following classifications have been employed:

A < 0.001 μ M

-360-

0.010 > B > 0.001 μ M

0.100 > C > 0.010 μ M

D > 0.1 μ M

"NA" = compound was not tested.

5

Anti-viral activity against Resistant Viruses

EP13 and D545701, two multi protease inhibitor resistant viruses were used to assess potency against mutant viruses. These viruses contain the following
10 mutations relative to the consensus sequence of wild type virus:

D545701-14: Protease amino acid sequence: L10I, L19Q, K20R, E35D, M36I, S37N, M46I, I50V, I54V, I62V, L63P,
15 A71V, V82A, L90M; reverse transcriptase amino acid sequence: E28K, K32E, V35I, T39S/T, E40D/V/Y/F, M41M/L, K43E, Y181Y/C

EP13: Protease amino acid sequence: M46I, L63P, A71V,
20 V82F/L, I84V; No reverse transcriptase mutations.

Reference data for the following protease inhibitors are (D545701-14; EP13):

Amprenavir™: >1000nM; 600nM
25 Indinavir™: 700nM; 560nM
Nelfinavir™: 690nM; N/A
Ritonavir™: >1000nM; >600nM
Saquinavir™: 900nM; N/A

30 Assays of the above mutant viruses were carried out as described above for the wild type virus and the results are shown below in Table B.

-361-

Table B

Compound No.	Wildtype virus - IC_{50}	EP13 mutant IC_{50}	D545701-14 mutant - IC_{50}
52	C	B	B
53	B	B	B
54	C	B	B
55	NA	B	B
201	NA	NA	NA
202	A	A	B
203	A	B	C
204	B	B	B
205	B	C	C
206	B	C	C
207	B	B	B
208	C	NA	NA
209	B	B	B
210	B	B	C
211	B	B	B
212	B	B	C
213	B	B	B
214	B	B	B
215	B	B	B
216	B	B	B
217	B	B	B
218	NA	NA	NA
219	B	B	B
220	NA	NA	NA
221	B	B	B
222	C	NA	NA
223	B	B	B
224	C	NA	NA
225	C	C	C

-362-

226	A	A	B
227	NA	NA	NA
228	C	NA	NA
229	C	B	B
230	C	B	B
231	B	B	B
232	B	B	NA
233	B	B	C
234	B	B	B
235	B	B	B
236	B	B	B
237	B	A	B
238	B	B	B
239	C	B	B
240	C	B	B
241	B	B	B
242	B	B	B
243	B	B	B
244	B	B	A
245	B	B	B
246	B	B	B
247	B	B	B
248	B	B	B
249	B	B	B
250	B	B	B
251	C	B	B
252	B	B	B
253	C	B	B
254	B	B	B
255	C	NA	NA
256	C	NA	NA
257	NA	NA	NA

-363-

258	C	NA	NA
259	C	B	B
260	B	B	B
261	B	B	B
262	B	B	B
263	B	B	B
264	C	C	NA
265	C	C	C
266	C	NA	NA
267	C	NA	NA
268	C	B	C
269	C	B	C
270	B	B	B
271	B	B	B
272	B	B	B
273	NA	NA	NA
274	C	B	C
275	C	B	C
276	NA	NA	NA
277	B	B	B
278	C	B	B
279	B	B	B
280	C	B	B
281	B	B	B
282	C	B	C
283	C	B	C
284	B	B	B
285	C	NA	NA
286	C	B	B
287	B	B	B
288	B	B	B
289	B	B	B

- 364 -

290	NA	NA	NA
291	NA	NA	NA
292	C	C	C
293	B	B	B
294	B	B	B
295	B	B	B
296	NA	NA	NA
297	C	C	NA
298	C	B	B
299	B	B	B
300	B	B	B
301	B	B	B
302	B	B	C
303	C	C	C
304	B	B	B
305	B	B	B
306	C	NA	NA
307	C	NA	NA
308	C	B	B
309	B	B	B
310	B	B	C
311	B	B	C
312	C	B	C
313	C	B	B
314	C	C	C
315	C	B	B
316	NA	NA	NA
317	B	B	B
318	B	B	B
319	B	B	B
320	B	B	B
321	B	B	B

-365-

322	B	B	B
323	B	B	B
324	B	B	B
325	C	NA	NA
326	B	C	C
327	NA	NA	NA
328	C	NA	NA
329	B	C	C
330	C	NA	NA
331	C	C	C
332	B	B	C
333	B	B	B
334	B	B	B
335	B	B	B
336	B	B	B
337	B	B	B
338	B	B	B
339	C	NA	NA
340	C	NA	NA
341	NA	NA	NA
342	C	C	C
343	NA	NA	NA
344	NA	NA	NA
345	NA	NA	NA
346	C	NA	NA
347	B	B	B
348	B	B	B
349	B	B	B
350	C	NA	NA
351	NA	NA	NA
352	A	A	B
353	A	A	B

-366-

354	C	NA	NA
355	C	C	C
356	B	B	A
357	C	B	C
358	C	C	C
359	C	C	C
360	NA	NA	NA
361	B	C	C
362	C	NA	NA
363	C	NA	NA
364	NA	NA	NA
365	B	B	B
366	B	B	B
367	A	A	B
368	A	A	B
369	B	NA	NA
370	A	B	B
371	C	B	C
372	B	B	C
373	B	B	C
374	B	B	B
375	B	B	C
376	B	C	C
377	B	B	C
378	B	B	C
379	B	B	B
380	B	B	C
381	B	B	B
382	B	B	B
383	B	B	B
384	B	B	B
385	B	B	C

-367-

386	B	B	C
387	B	B	B
388	B	B	B
389	B	B	B
390	B	B	C
391	B	B	B
392	B	B	B
393	C	C	C
394	B	B	B
395	B	B	B
396	B	B	B
397	C	B	B
398	NA	NA	NA
399	NA	NA	NA
400	NA	NA	NA

In Table B, the following classifications have been employed:

A < 0.001 μ M

5 0.010 > B > 0.001 μ M

0.100 > C > 0.010 μ M

D > 0.1 μ M

"NA" = compound was not tested.

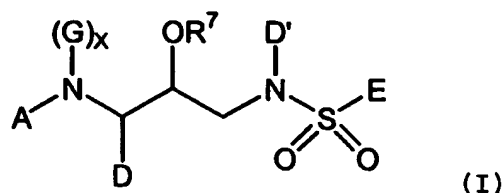
10 While we have hereinbefore presented a number of
embodiments of this invention, it is apparent that our
basic construction can be altered to provide other
embodiments which utilize the methods of this invention.
Therefore, it will be appreciated that the scope of this
15 invention is to be defined by the claims appended hereto
rather than the specific embodiments which have been
presented hereinbefore by way of example.

-368-

CLAIMS

We claim:

- 5 1. A compound of the formula (I):



and pharmaceutically acceptable salts thereof;

wherein:

- 10 A is selected from H; Ht; $-R^1\text{-Ht}$; $-R^1\text{-C}_1\text{-C}_6$ alkyl, which is optionally substituted with one or more groups independently selected from hydroxy, $-\text{CN}$, $\text{C}_1\text{-C}_4$ alkoxy, Ht, $-\text{O-Ht}$, $-\text{NR}^2\text{-Ht}$, $-\text{NR}^2\text{-CO-N(R}^2\text{)}_2$, $-\text{SO}_2\text{-N(R}^2\text{)}_2$, $-\text{SO}_2\text{-R}^2$ or $-\text{CO-N(R}^2\text{)}_2$; $-R^1\text{-C}_2\text{-C}_6$ alkenyl, which is optionally
- 15 substituted with one or more groups independently selected from hydroxy, $\text{C}_1\text{-C}_4$ alkoxy, Ht, $-\text{O-Ht}$, $-\text{NR}^2\text{-CO-N(R}^2\text{)}_2$ or $-\text{CO-N(R}^2\text{)}_2$; or R^7 ;

- each R^1 is independently selected from $-\text{C(O)-}$, $-\text{S(O)}_2\text{-}$, $-\text{C(O)-C(O)-}$, $-\text{O-C(O)-}$, $-\text{O-S(O)}_2\text{-}$, $-\text{NR}^2\text{-}$, $-\text{NR}^2\text{-S(O)}_2\text{-}$, $-\text{NR}^2\text{-C(O)-}$ or $-\text{NR}^2\text{-C(O)-C(O)-}$;
- 20

- each Ht is independently selected from $\text{C}_3\text{-C}_7$ cycloalkyl; $\text{C}_5\text{-C}_7$ cycloalkenyl; $\text{C}_6\text{-C}_{14}$ aryl; or a 5-7 membered saturated or unsaturated heterocycle, containing one or more heteroatoms selected from N, $\text{N(R}^2\text{)}$, O, S and S(O)_n ; wherein said aryl or said heterocycle is optionally
- 25 fused to Q; and wherein any member of said Ht is optionally substituted with one or more substituents independently selected from oxo, $-\text{OR}^2$, SR^2 , $-\text{R}^2$, $-\text{N(R}^2\text{)(R}^2\text{)}$, $-\text{R}^2\text{-OH}$, $-\text{CN}$, $-\text{CO}_2\text{R}^2$, $-\text{C(O)-N(R}^2\text{)}_2$, $-\text{S(O)}_2\text{-N(R}^2\text{)}_2$,

-369-

$-N(R^2)-C(O)-R^2$, $-N(R^2)-C(O)O-R^2$, $-C(O)-R^2$, $-S(O)_n-R^2$, $-OCF_3$,
 $-S(O)_n-Q$, methylenedioxy, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$,
 $-NO_2$, Q , $-OQ$, $-OR^7$, $-SR^7$, $-R^7$, $-N(R^2)(R^7)$ or $-N(R^7)_2$;

each R^2 is independently selected from H, or C_1-C_4
 5 alkyl optionally substituted with a 3-7 membered
 saturated, partially saturated or unsaturated carbocyclic
 ring system; or a 5-7 membered saturated, partially
 saturated or unsaturated heterocyclic ring containing one
 or more heteroatoms selected from O, N, S, $S(O)_n$ or
 10 $N(R^{33})$; wherein any of said ring systems or $N(R^{33})$ is
 optionally substituted with 1 to 4 substituents
 independently selected from $-X'-Y'$, $-O$ -arylalkyl,
 $-S$ -arylalkyl, $-N(Y')_2$, $-N(H)$ -arylalkyl, $-N(C_1-C_4$
 alkyl)-arylalkyl, oxo, $-O-(C_1-C_4$ alkyl), OH, C_1-C_4 alkyl,
 15 $-SO_2H$, $-SO_2-(C_1-C_4$ alkyl), $-SO_2-NH_2$, $-SO_2-NH(C_1-C_4$ alkyl),
 $-SO_2-N(C_1-C_4$ alkyl) $_2$, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_4$
 alkyl) $_2$, $-NH-C(O)H$, $-N(C_1-C_4$ alkyl)- $C(O)H$, $-NH-C(O)-C_1-C_4$
 alkyl, $-C_1-C_4$ alkyl-OH, -OH, -CN, $-C(O)OH$, $-C(O)O-C_1-C_4$
 alkyl, $-C(O)-NH_2$, $-C(O)-NH(C_1-C_4$ alkyl), $-C(O)-N(C_1-C_4$
 20 alkyl) $_2$, halo or $-CF_3$;

X' is $-O-$, $-S-$, $-NH-$, $-NHC(O)-$, $-NHC(O)O-$, $-NHSO_2-$,
 or $-N(C_1-C_4)$ alkyl-;

Y' is C_1-C_{15} alkyl, C_2-C_{15} alkenyl or alkynyl, wherein
 one to five carbon atoms in Y are optionally substituted
 25 with C_3-C_7 cycloalkyl or C_5-C_6 cycloalkenyl, C_6-C_{14} aryl or
 a 5-7 membered saturated or unsaturated heterocycle,
 containing one or more heteroatoms selected from N, NH,
 O, S and $S(O)_n$;

each R^3 is independently selected from H, Ht, C_1-C_6
 30 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or
 C_5-C_6 cycloalkenyl; wherein any member of said R^3 , except
 H, is optionally substituted with one or more

-370-

substituents selected from $-OR^2$, $-C(O)-N(R^2)_2$,
 $-S(O)_n-N(R^2)_2$, $-N(R^2)_2$, $-N(R^2)-C(O)O(R^2)$, $-N(R^2)-C(O)N(R^2)_2$,
 $-N(R^2)-C(O)-R^2$, Ht, $-CN$, $-SR^2$, $-C(O)OR^2$, $N(R^2)-C(O)-R^2$;

each R^{33} is selected from H, C_1-C_6 alkyl, C_2-C_6

- 5 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl or C_5-C_6
cycloalkenyl, C_6-C_{14} aryl or a 5-7 membered saturated or
unsaturated heterocycle, containing one or more
heteroatoms selected from N, NH, O, S and $S(O)_n$;

each n is independently 1 or 2;

- 10 G, when present, is selected from H, R^7 or C_1-C_4
alkyl, or, when G is C_1-C_4 alkyl, G and R^7 are bound to one
another either directly or through a C_1-C_3 linker to form
a heterocyclic ring; or

when G is not present (i.e., when x in $(G)_x$ is 0),

- 15 then the nitrogen to which G is attached is bound
directly to the R^7 group in $-OR^7$ with the concomitant
displacement of one $-ZM$ group from R^7 ;

D is selected from C_1-C_6 alkyl which is substituted
with Q, which is optionally substituted with one or more

- 20 groups selected from C_3-C_6 cycloalkyl, $-R^3$, $-O-Q$ or Q;
 C_2-C_4 alkenyl which is substituted with Q, which is
optionally substituted with one or more groups selected
from $-OR^2$, $-S-Ht$, $-R^3$, $-O-Q$ or Q; C_3-C_6 cycloalkyl, which
is optionally substituted with or fused to Q; or C_5-C_6
25 cycloalkenyl, which is optionally substituted with or
fused to Q;

each Q is independently selected from a 3-7 membered
saturated, partially saturated or unsaturated carbocyclic
ring system; or a 5-7 membered saturated, partially
30 saturated or unsaturated heterocyclic ring containing one
or more heteroatoms selected from O, N, S, $S(O)_n$ or $N(R^2)$;
wherein Q contains one substituent selected from $-OR^2$, -

-371-

OR⁸, -O-arylalkyl, -SR⁸, -S-arylalkyl, -N(R²)R⁸, -
 N(R²)-arylalkyl and may be optionally substituted with one
 or more additional substituents independently selected
 from oxo, -OR⁸, -O-arylalkyl -SR⁸, -S-arylalkyl, -N(R²)R⁸,
 5 -N(R²)-arylalkyl, -OR², -R², -SO₂R², -SO₂-N(R²)₂, -N(R²)₂,
 -N(R²)-C(O)-R², -OH, (C₁-C₄)-OH, -CN, -CO₂R², -C(O)-N(R²)₂,
 halo or -CF₃;

each R⁸ is independently selected from Ht, -C₁-C₁₅
 branched or straight chain alkyl, alkenyl or alkynyl
 10 wherein one to five carbon atoms in said alkyl, alkenyl
 or alkynyl are independently replaced by W, or wherein
 one to five carbon atoms in said alkyl, alkenyl or
 alkynyl are substituted with Ht; and wherein R⁸ is
 additionally and optionally substituted with one or more
 15 groups independently selected from -OH, -S(C₁-C₆ alkyl), -
 CN, -CF₃, -N(R²)₂, halo, -C₁-C₄-alkyl, -C₁-C₄-alkoxy; -Ht;
 -O-Ht; -NR²-CO-N(R²)₂; -CO-N(R²)₂; -R¹-C₂-C₆ alkenyl, which
 is optionally substituted with one or more groups
 independently selected from hydroxy, C₁-C₄ alkoxy, Ht,
 20 -O-Ht, -NR²-CO-N(R²)₂ or -CO-N(R²)₂; or R⁷;

wherein W is -O-, -NR²-, -S-, -C(O)-, -C(S)-,
 -C(=NR²)-, -S(O)₂-, -NR²-S(O)₂-, -S(O)₂-NR²-, -NR²-C(O)O-, -
 O-C(O)NR²-, -NR²-C(O)NR²-, -NR²-C(S)NR²-, -CONR², -NR²C(O)-,
 -C(S)NR², -NR²C(S)-, -NR²-C(=N-CN)-NR²-, -NR²C(=N-CN)O- or
 25 -C(O)O-;

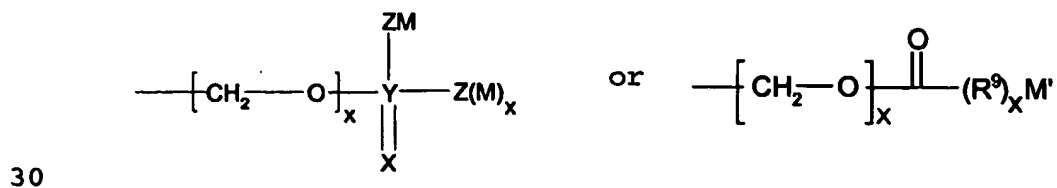
D' is selected from C₁-C₁₅ alkyl, C₁-C₁₅ alkoxy, C₂-C₁₅
 alkenyl, C₂-C₁₅ alkenyloxy, C₂-C₁₅ alkynyl, or C₂-C₁₅
 alkynyloxy, wherein D' optionally comprises one or more
 substituents independently selected from Ht, oxo, halo,
 30 -CF₃, -OCF₃, -NO₂, azido, -SH, -SR³, -N(R³)-N(R³)₂,
 -O-N(R³)₂, -(R³)N-O-(R³), -N(R³)₂, -CN, -CO₂R³, -C(O)-N(R³)₂,
 -S(O)_n-N(R³)₂, -N(R³)-C(O)-R³, -N(R³)-C(O)-N(R³)₂, -C(O)-R³,

-372-

- $-S(O)_n-R^3$, $-N(R^3)-S(O)_n(R^3)$, $-N(R^3)-S(O)_n-N(R^3)_2$,
 $-S-NR^3-C(O)R^3$, $-C(S)N(R^3)_2$, $-C(S)R^3$, $-NR^3-C(O)OR^3$,
 $-O-C(O)OR^3$, $-O-C(O)N(R^3)_2$, $-NR^3-C(S)R^3$, $=N-OH$, $=N-OR^3$,
 $=N-N(R^3)_2$, $=NR^3$, $=NNR^3C(O)N(R^3)_2$, $=NNR^3C(O)OR^3$,
5 $=NNR^3S(O)_n-N(R^3)_2$, $-NR^3-C(S)OR^3$, $-NR^3-C(S)N(R^3)_2$,
 $-NR^3-C[=N(R^3)]-N(R^3)_2$, $-N(R^3)-C[=N-NO_2]-N(R^3)_2$,
 $-N(R^3)-C[=N-NO_2]-OR^3$, $-OC(O)R^3$, $-OC(S)R^3$, $-OC(O)N(R^3)_2$,
 $-C(O)N(R^3)-N(R^3)_2$, $-N(R^3)-N(R^3)C(O)R^3$, $-N(R^3)-OC(O)R^3$,
 $-N(R^3)-OC(O)R^3$, $-N(R^3)-OC(O)R^3$, $-OC(S)N(R^3)_2$,
10 $-OC(S)N(R^3)(R^3)$, or $-PO_3-R^3$;

- E is selected from Ht; O-Ht; Ht-Ht; Ht fused with
 Ht; $-O-R^3$; $-N(R^2)(R^3)$; $-N(R^2)-Ht$; C_1-C_6 alkyl, which is
 optionally substituted with one or more groups selected
 from R^4 or Ht; C_2-C_6 alkenyl, which is optionally
 15 substituted with one or more groups selected from R^4 or
 Ht; C_3-C_6 saturated carbocycle, which is optionally
 substituted with one or more groups selected from R^4 or
 Ht; or C_5-C_6 unsaturated carbocycle, which is optionally
 substituted with one or more groups selected from R^4 or
 20 Ht;

- each R^4 is independently selected from $-R^2$, $-OR^2$,
 $-OR^3$, $-SR^2$, $-SOR^2$, $-SO_2R^2$, $-CO_2R^2$, $-OC(O)-R^2$, $-C(O)-N(R^2)_2$,
 $-C(O)-NR^2(OR^2)$, $-S(O)_2-N(R^2)_2$, halo, $-NR^2-C(O)-R^2$, $-NR^2-OR^2$,
 $-N(R^2)_2$ or $-CN$;
 25 each R^7 is independently selected from hydrogen,



wherein each M is independently selected

-373-

from H, Li, Na, K, Mg, Ca, Ba, $-N(R^2)_4$, C_1 - C_{12} -alkyl, C_2 - C_{12} -alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group, other than the $-CH_2$ that is bound to Z, is optionally replaced by a heteroatom group
 5 selected from O, S, $S(O)$, $S(O)_2$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-C_1$ - C_4 alkyl, $-N(R^2)_2$, $-N(R^2)_3$, $-OH$, $-O-(C_1-C_4 \text{ alkyl})$, $-CN$, $-C(O)OR^2$, $-C(O)-N(R^2)_2$, $S(O)_2-N(R^2)_2$, $-N(R^2)-C(O)-R_2$,
 10 $C(O)R^2$, $-S(O)_n-R^2$, $-OCF_3$, $-S(O)_n-R^6$, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

M' is H, C_1 - C_{12} -alkyl, C_2 - C_{12} -alkenyl, or $-R^6$; wherein 1 to 4 $-CH_2$ radicals of the alkyl or alkenyl group is optionally replaced by a heteroatom group selected from
 15 O, S, $S(O)$, $S(O)_2$, or $N(R^2)$; and wherein any hydrogen in said alkyl, alkenyl or R^6 is optionally replaced with a substituent selected from oxo, $-OR^2$, $-C_1$ - C_4 alkyl, $-N(R^2)_2$, $N(R^2)_3$, $-OH$, $-O-(C_1-C_4 \text{ alkyl})$, $-CN$, $-C(O)OR^2$, $-C(O)-N(R^2)_2$, $-S(O)_2-N(R^2)_2$, $-N(R^2)-C(O)-R_2$, $-C(O)R^2$, $-S(O)_n-R^2$, $-OCF_3$,
 20 $-S(O)_n-R^6$, $-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, or $-NO_2$;

x is 0 or 1;

Z is O, S, $N(R^2)_2$, or, when M is not present, H.

Y is P or S;

X is O or S; and

25 R^9 is $C(R^2)_2$, O or $N(R^2)$; and wherein when Y is S, Z is not S; and

R^6 is a 5-6 membered saturated, partially saturated or unsaturated carbocyclic or heterocyclic ring system, or an 8-10 membered saturated, partially saturated or
 30 unsaturated bicyclic ring system; wherein any of said heterocyclic ring systems contains one or more heteroatoms selected from O, N, S, $S(O)_n$ or $N(R^2)$; and

-374-

wherein any of said ring systems optionally contains 1 to 4 substituents independently selected from -OH, -C₁-C₄ alkyl, -O-(C₁-C₄ alkyl) or -O-C(O)-(C₁-C₄ alkyl).

- 5 2. The compound according to claim 1, wherein R⁸ is -C₁-C₄-branched or straight chain alkyl, wherein one to two carbon atoms in said alkyl are independently replaced by W, wherein R⁸ is additionally and optionally substituted with one or more groups independently
- 10 selected from -OH; -C₁-C₄-alkoxy; -Ht; -O-Ht; -NR²-CO-N(R²)₂; -CO-N(R²)₂; -R¹-C₂-C₆ alkenyl, which is optionally substituted with one or more groups independently selected from hydroxy, C₁-C₄ alkoxy, Ht, -O-Ht, -NR²-CO-N(R²)₂ or -CO-N(R²)₂; or R⁷;
- 15 wherein W is -O-, -NR²-, -NR²-S(O)₂-, -NR²-C(O)O-, -O-C(O)NR²-, -NR²-C(O)NR²-, -NR²-C(S)NR²-, -NR²C(O)-, -C(=NR²)-, -C(O)NR²-, -NR²-C(=N-CN)-NR²-, -NR²C(=N-CN)O- or -C(O)O-; and

wherein Ht, R¹, R² and R⁷ are as defined in claim 1.

20

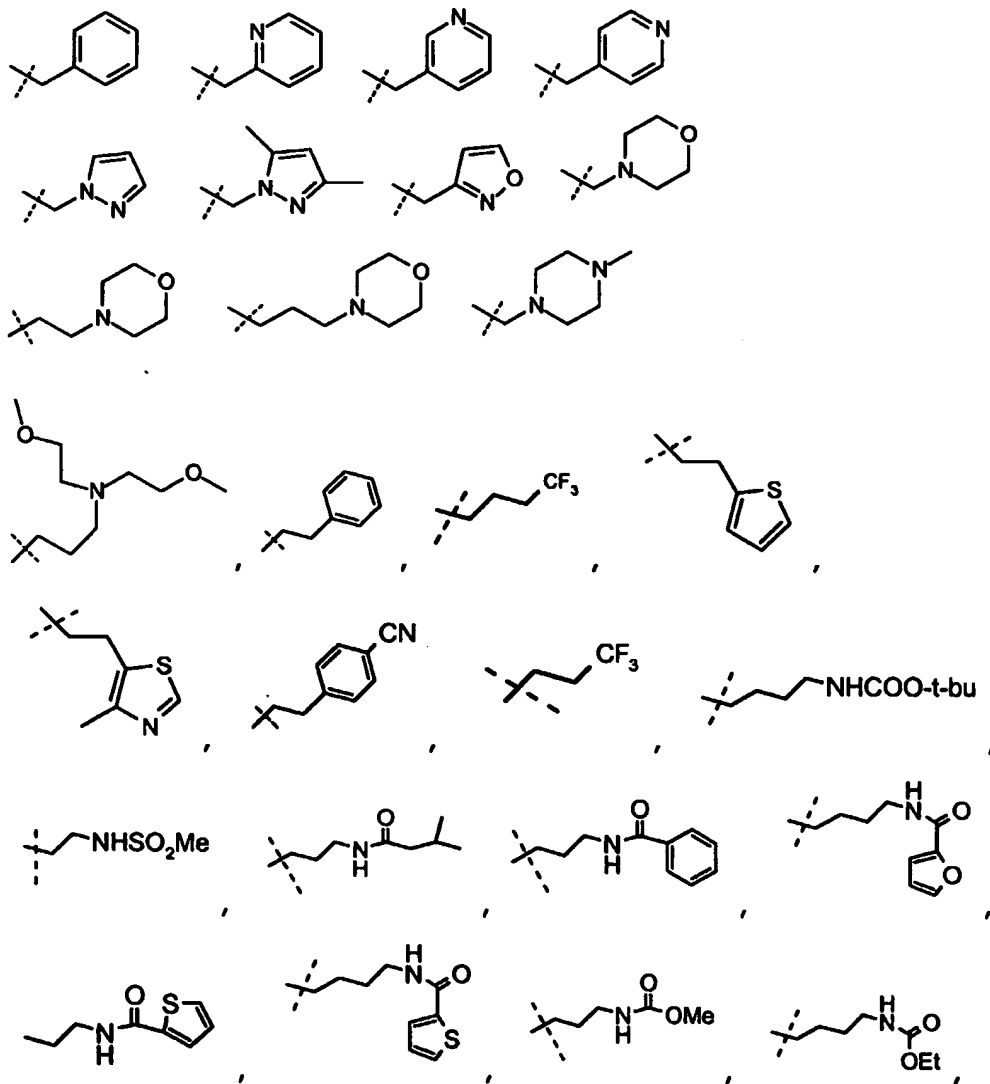
3. The compound according to claim 1, wherein R⁸ is a -C₁-C₄-branched or straight alkyl chain, wherein one to two carbon atoms are substituted with Ht;

- wherein Ht is C₆₋₁₄ aryl or a 5-7 membered saturated
- 25 or unsaturated heterocycle, containing one or more heteroatoms selected from N, N(R²), O, S and S(O)_n, wherein any member of Ht is optionally substituted with one or more substituents independently selected from oxo, -OR², SR², -R², -N(R²)(R²), -R²-OH, -CN, -CO₂R²,
- 30 -C(O)-N(R²)₂, -S(O)₂-N(R²)₂, -N(R²)-C(O)-R², -N(R²)-C(O)O-R², -C(O)-R², -S(O)_n-R², -OCF₃, -S(O)_n-Q, methylenedioxy,

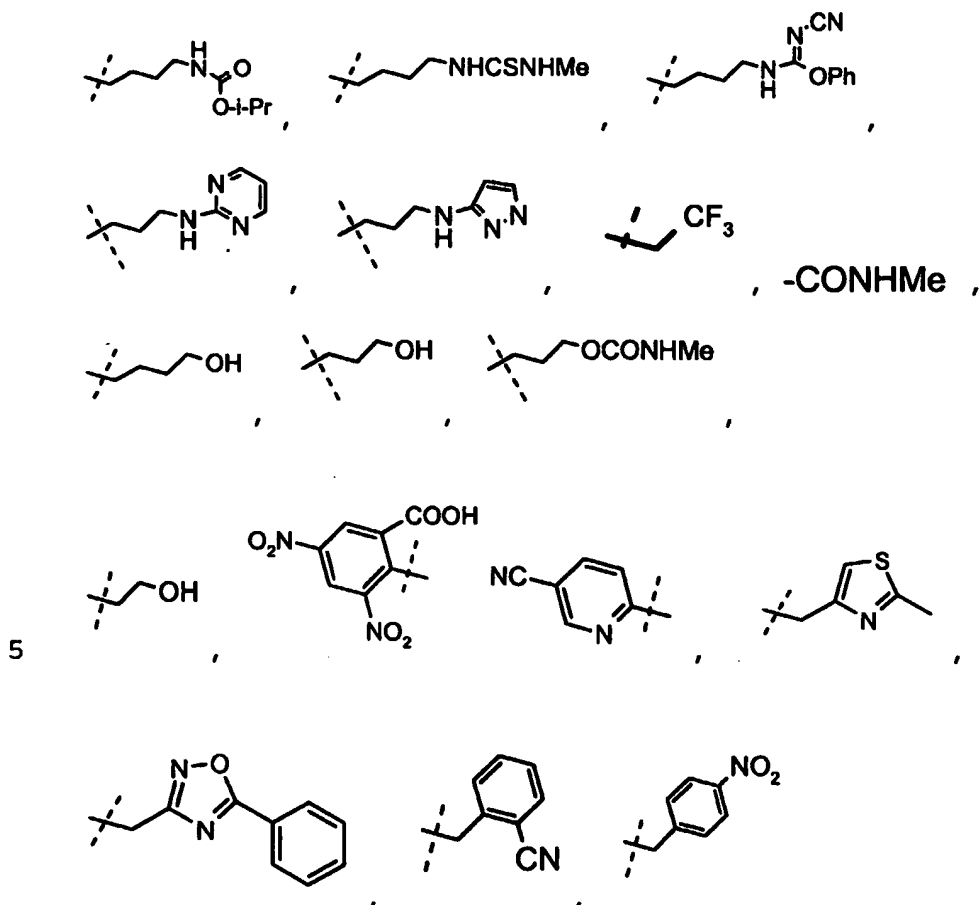
-375-

$-N(R^2)-S(O)_2(R^2)$, halo, $-CF_3$, $-NO_2$, Q, $-OQ$, $-OR^7$, $-SR^7$, $-R^7$,
 $-N(R^2)(R^7)$ or $-N(R^7)_2$;

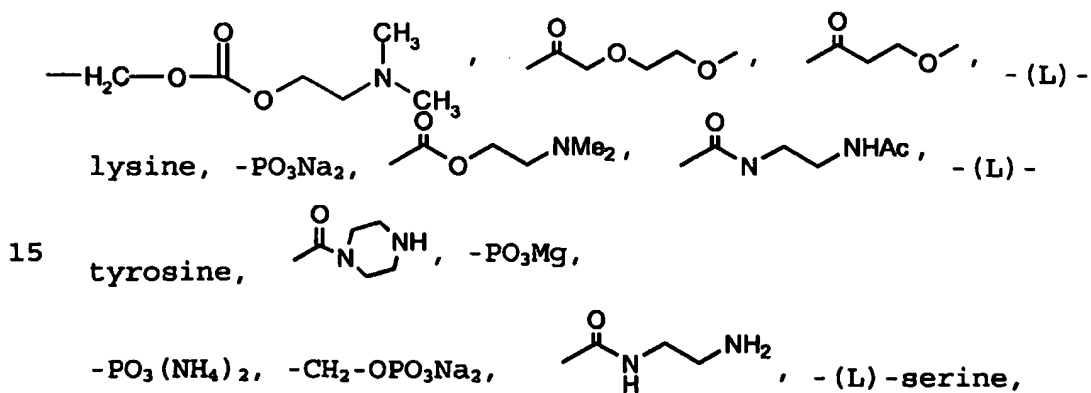
4. The compound according to claim 1, wherein R^8 is
 5 selected from:



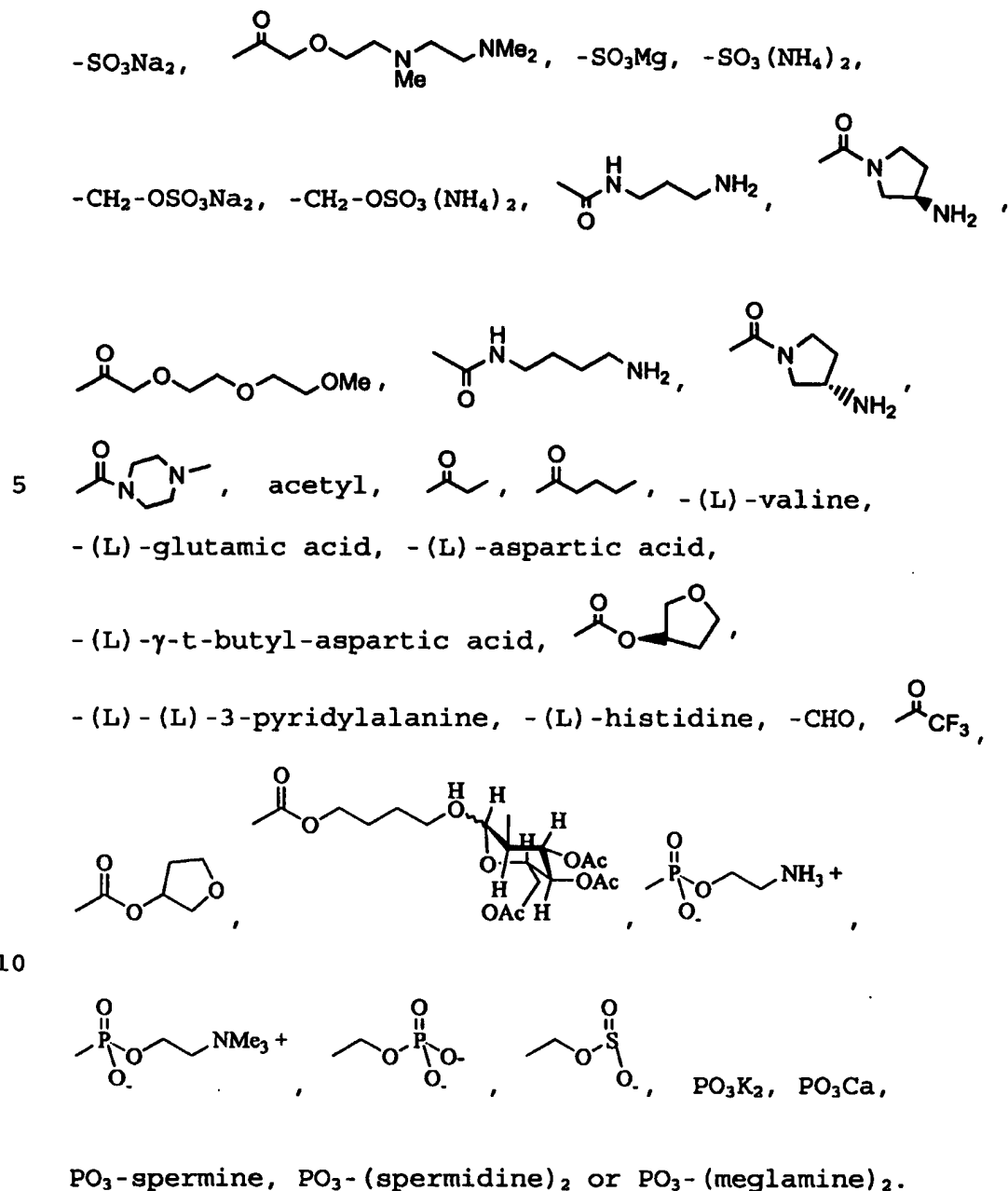
-376-



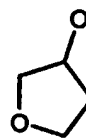
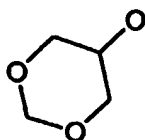
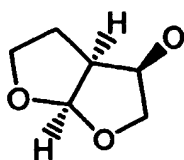
- 10 5. The compound according to claim 1, wherein at least one R⁷ is selected from:



-377-



- 15 6. The compound according to claim 1, wherein:
 A is $\text{R}'-\text{C}(\text{O})$, wherein R' is selected from $-\text{C}_1-\text{C}_6$ alkyl,



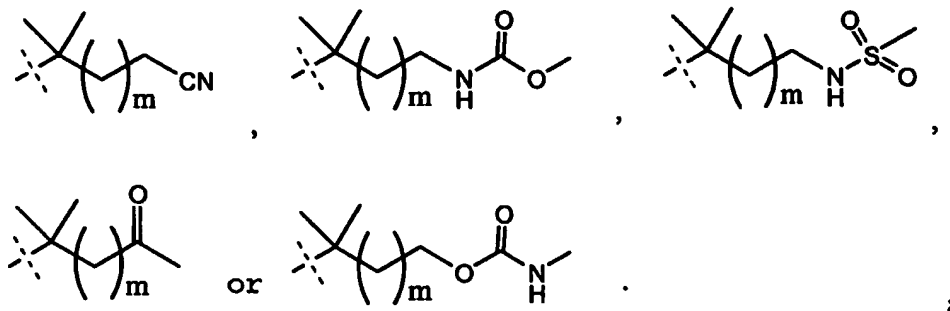
-378-

or

7. The compound according to claim 1, wherein:

D' is $-\text{CH}_2-\text{R}''$, wherein R'' is selected from:

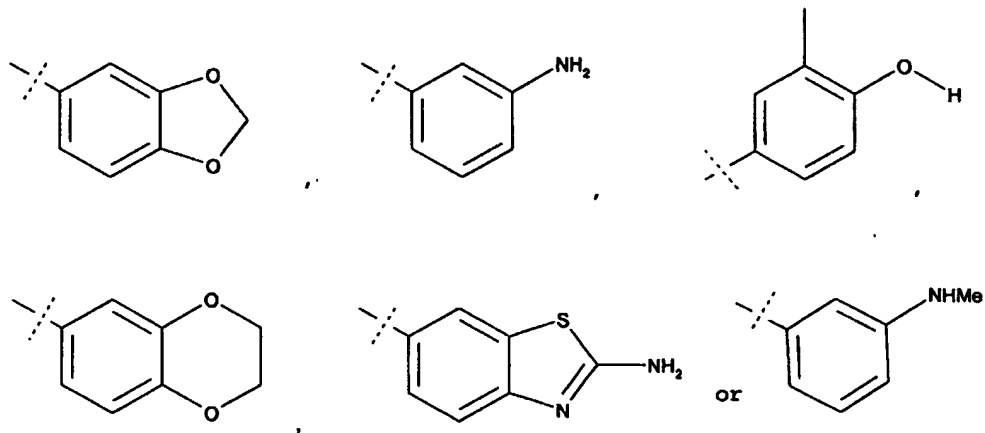
5 isobutyl,



wherein m is 0 to 3.

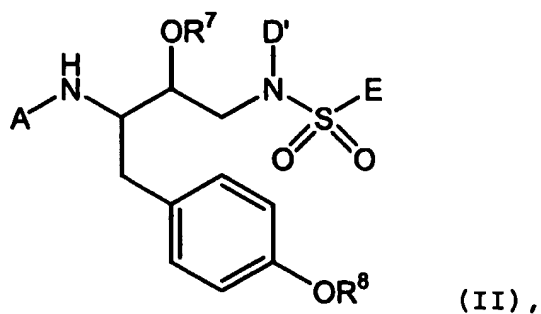
8. The compound according to claim 1, wherein:

10 E is selected from:



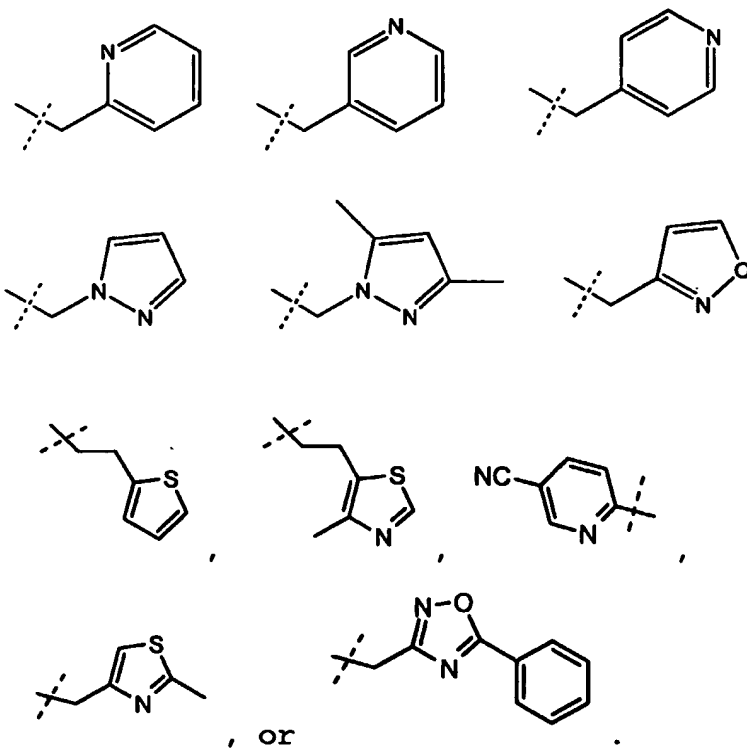
9. The compound according to claim 1, having the formula (II):

-379-



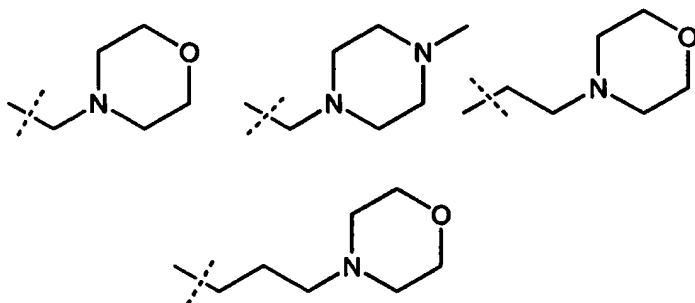
wherein A, R⁷, D', R⁸ and E are as defined in claim 1.

- 5 10. The compound according to claim 9, wherein R⁸ is selected from:

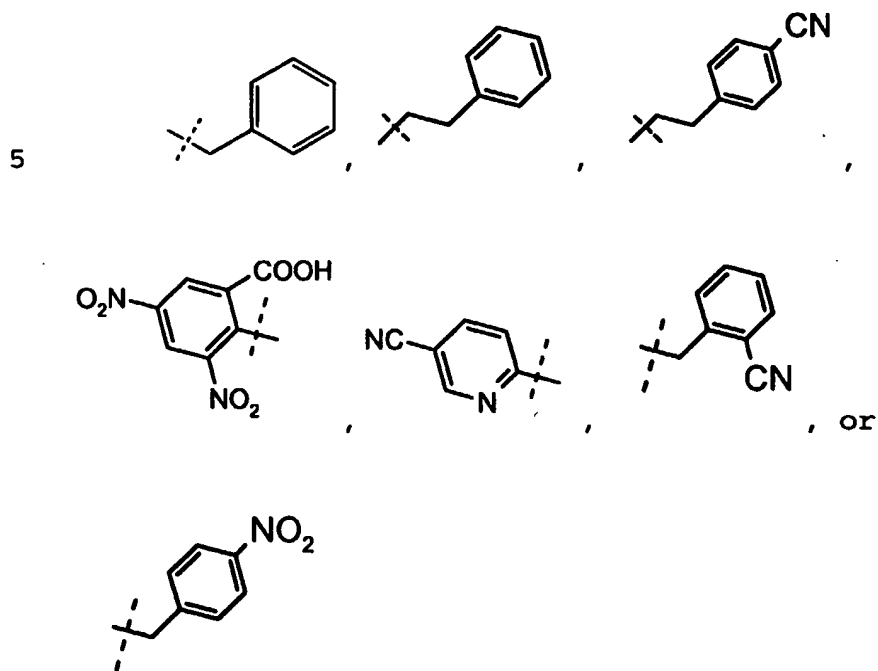


11. The compound according to claim 9, wherein R⁸ is selected from:

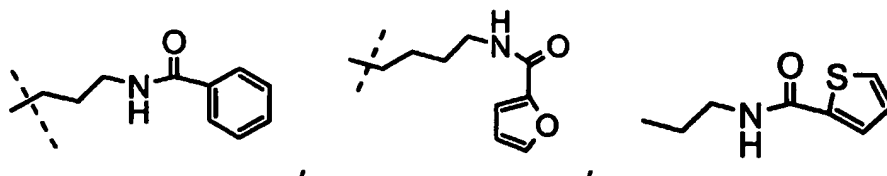
-380-



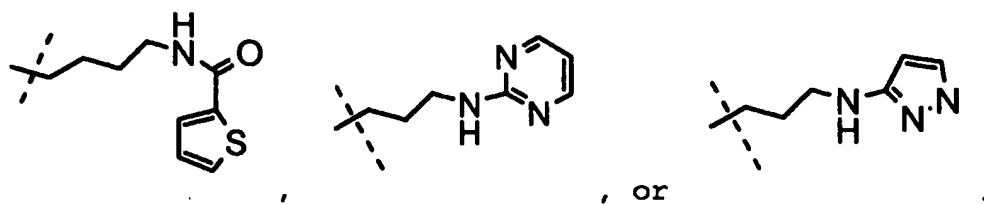
12. The compound according to claim 9, wherein R⁸ is selected from:



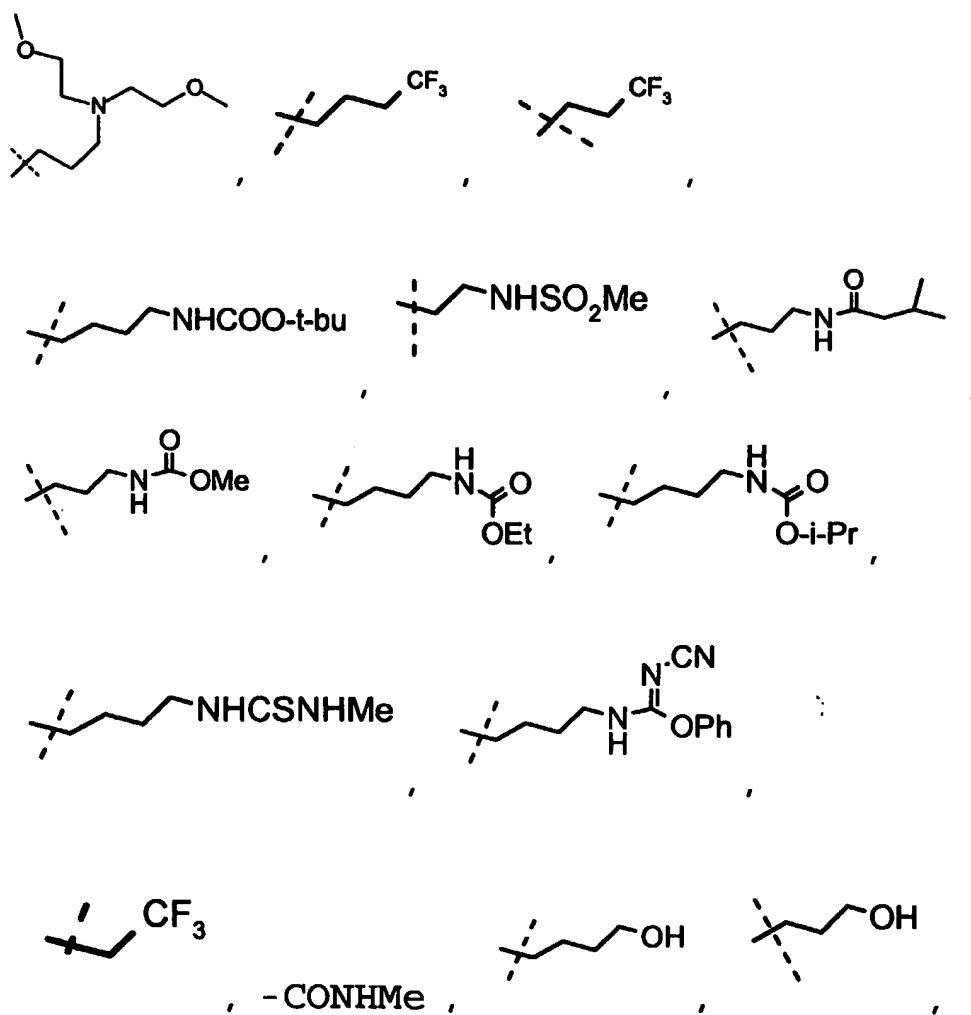
13. The compound according to claim 9, wherein R⁸ is selected from:



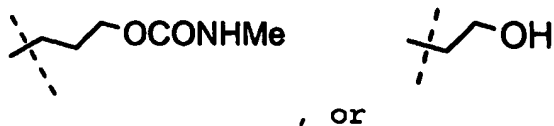
-381-



14. The compound according to claim 9, wherein R⁸ is
5 selected from:



-382-



15. The compound according to claim 9, wherein said compound is selected from compound numbers: 18, 19, 20,
5 22, 24, 25, 26, 27, 31, 33, 35, 36, 38, 41, 43, 48, 49,
51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 68, 69, 71, 72,
73, 74, 202-204, 209, 213, 215, 217, 223, 227, 231, 233,
236, 237, 239, 243, 247, 250, 260, 263, 271, 281, 289,
293, 295, 304, 309, 317, 319, 320, 322, 334, 335, 348,
10 364, 367, 368, 375, 382, 383 and 396.

16. The compound according to claim 15, wherein said compound is selected from compound numbers: 26, 27,
31, 33, 35, 36, 38, 41, 43, 48, 49, 51, 52, 53, 54, 55,
15 56, 57, 58, 59, 60, 69, 71, 72, 73, 74, 209, 215, 227,
233, 237, 281, 289, 295, 304, 309, 322, 335, 364, 368,
382 and 383.

17. The compound according to claim 16, wherein
20 said compound is selected from: 54, 209, 237, 281, 295,
309, 367 and 368.

18. A composition comprising a compound according to any one of claims 1 to 17, in an amount sufficient to
25 inhibit an aspartyl protease; and a pharmaceutically acceptable carrier.

19. The composition according to claim 18, wherein said composition is in a pharmaceutically acceptable form
30 for administration to a human being.

-383-

20. The composition according to claim 18, wherein said composition additionally comprises an additional anti-viral agent.

5

21. The composition according to claim 18, wherein said composition comprises at least one additional therapeutic agent selected from (1 alpha, 2 beta, 3 alpha)-9-[2,3-bis(hydroxymethyl)cyclobutyl]-guanine ((-)BHCG, SQ-34514); oxetanocin-G (3,4-bis-(hydroxymethyl)-2-oxetanosyl]guanine); acyclic nucleosides, such as acyclovir, valaciclovir, famciclovir, ganciclovir or penciclovir; acyclic nucleoside phosphonates, such as (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC); ribonucleotide reductase inhibitors, such as 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl]thiocarbonohydrazone, 3'-azido-3'-deoxythymidine; other 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, or 2',3'-didehydrothymidine; other aspartyl protease inhibitors, such as indinavir, ritonavir, nelfinavir, or [3S-[3R*(1R*, 2S*)]]-[3[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-tetrahydro-3-furanyl ester (amprenavir); oxathiolane nucleoside analogues, such as (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine) or cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC); 3'-deoxy-3'-fluorothymidine; 5-chloro-2',3'-dideoxy-3'-fluorouridine; (-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol; ribavirin; 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G); tat inhibitors,

10
15
20
25
30

-384-

such as 7-chloro-5-(2-pyrrolyl)-3H-1,4-benzodiazepin-2-(H)one (Ro5-3335) or 7-chloro-1,3-dihydro-5-(1H-pyrrolyl)-3H-1,4-benzodiazepin-2-amine (Ro24-7429);

interferons, such as α -interferon; renal excretion

5 inhibitors such as probenecid; nucleoside transport inhibitors such as dipyrindamole; pentoxifylline; N-acetylcysteine (NAC); Procysteine; α -trichosanthin; phosphonoformic acid; immunomodulators, such as interleukin II or thymosin; granulocyte macrophage colony

10 stimulating factors; erythropoietin; soluble CD₄ and genetically engineered derivatives thereof; non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as nevirapine (BI-RG-587), zalcitabine (α -APA) or delaviridine (BHAP); phosphonoformic acid; 1,4-dihydro-

15 2H-3,1-benzoxazin-2-ones NNRTIs, such as (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (L-743,726 or DMP-266); or quinoxaline NNRTIs, such as isopropyl (2S)-7-fluoro-3,4-dihydro-2-ethyl-3-oxo-1(2H)-quinoxalinecarboxylate (HBY1293).

20

22. The composition according to any one of claims 18-21, wherein said composition is in an orally available dosage form.

25

23. A method of treating a patient infected with a virus that depends upon an aspartyl protease for an obligatory event in its life cycle comprising the step of administering to said patient a composition according to claim 18.

30

24. A method of treating a patient infected with HIV-I or HIV-II comprising the step of administering to

-385-

said patient a composition according to claim 18.

25. The method according to claim 23 or 24, comprising the additional step of administering to said
5 patient an additional therapeutic agent selected from (1 alpha, 2 beta, 3 alpha)-9-[2,3-bis(hydroxymethyl) cyclobutyl]guanine [(-)BHCG, SQ-34514]; oxetanocin-G (3,4-bis-(hydroxymethyl)-2-oxetanosyl]guanine); acyclic nucleosides, such as acyclovir, valaciclovir,
10 famciclovir, ganciclovir or penciclovir; acyclic nucleoside phosphonates, such as (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC); ribonucleotide reductase inhibitors, such as 2-acetylpyridine 5-[(2-chloroanilino)thiocarbonyl] thiocarbonohydrazone,
15 3'-azido-3'-deoxythymidine; other 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, or 2',3'-didehydrothymidine; other aspartyl protease inhibitors, such as indinavir, ritonavir, nelfinavir, or [3S-[3R*(1R*, 2S*)]]-[3[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-
20 (phenylmethyl)propyl]-tetrahydro-3-furanyl ester (amprenavir); oxathiolane nucleoside analogues, such as (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-cytosine (lamivudine) or cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC); 3'-deoxy-3'-
25 fluoro-thymidine; 5-chloro-2',3'-dideoxy-3'-fluorouridine; (-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol; ribavirin; 9-[4-hydroxy-2-(hydroxymethyl)but-1-yl]-guanine (H2G); tat inhibitors,
30 such as 7-chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2-(H)one (Ro5-3335) or 7-chloro-1,3-dihydro-5-(1H-pyrrol-2-yl)-3H-1,4-benzodiazepin-2-amine (Ro24-7429);

-386-

interferons, such as α -interferon; renal excretion inhibitors such as probenecid; nucleoside transport inhibitors such as dipyridamole; pentoxifylline; N-acetylcysteine (NAC); Procysteine; α -trichosanthin;
5 phosphonoformic acid; immunomodulators, such as interleukin II or thymosin; granulocyte macrophage colony stimulating factors; erythropoietin; soluble CD₄ and genetically engineered derivatives thereof; non-nucleoside reverse transcriptase inhibitors (NNRTIs),
10 such as nevirapine (BI-RG-587), zidovudine (ZDV) or delaviridine (BHAP); phosphonoformic acid; 1,4-dihydro-2H-3,1-benzoxazin-2-ones NNRTIs, such as (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (L-743,726 or DMP-266); or quinoxaline
15 NNRTIs, such as isopropyl (2S)-7-fluoro-3,4-dihydro-2-ethyl-3-oxo-1(2H)-quinoxalinecarboxylate (HBY1293), wherein said additional agent is administered to said patient as either a separate dosage form or as a single dosage form together with said compound.

20

26. A method of treating a patient diagnosed with AIDS; AIDS related complex (ARC); progressive generalized lymphadenopathy (PGL); Kaposi's sarcoma, thrombocytopenic purpura; AIDS-related neurological conditions such as
25 AIDS dementia complex, multiple sclerosis or tropical paraperesis; anti-HIV antibody-positive conditions; or HIV-positive conditions, comprising the step of administering to said patient a composition according to claim 18.

30

27. The method according to claim 26, comprising the additional step of administering to said patient an

-387-

additional therapeutic agent selected from (1 alpha, 2 beta, 3 alpha)-9-[2,3-bis(hydroxymethyl) cyclobutyl]guanine [(-)BHCG, SQ-34514]; oxetanocin-G (3,4-bis-(hydroxymethyl)-2-oxetanosyl]guanine); acyclic
5 nucleosides, such as acyclovir, valaciclovir, famciclovir, ganciclovir or penciclovir; acyclic nucleoside phosphonates, such as (S)-1-(3-hydroxy-2-phosphonyl-methoxypropyl)cytosine (HPMPC); ribonucleotide reductase inhibitors, such as 2-acetylpyridine 5-[(2-
10 chloroanilino)thiocarbonyl) thiocarbonohydrazone, 3'-azido-3'-deoxythymidine; other 2',3'-dideoxynucleosides such as 2',3'-dideoxycytidine, 2',3'-dideoxyadenosine, 2',3'-dideoxyinosine, or 2',3'-didehydrothymidine; other aspartyl protease inhibitors, such as indinavir,
15 ritonavir, nelfinavir, or [3S-[3R*(1R*, 2S*)]]-[3[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-tetrahydro-3-furanyl ester (amprenavir); oxathiolane nucleoside analogues, such as (-)-cis-1-(2-hydroxymethyl)-1,3-oxathiolane 5-yl)-
20 cytosine (lamivudine) or cis-1-(2-(hydroxymethyl)-1,3-oxathiolan-5-yl)-5-fluorocytosine (FTC); 3'-deoxy-3'-fluorothymidine; 5-chloro-2',3'-dideoxy-3'-fluorouridine; (-)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol; ribavirin; 9-[4-hydroxy-2-
25 (hydroxymethyl)but-1-yl]-guanine (H2G); tat inhibitors, such as 7-chloro-5-(2-pyrryl)-3H-1,4-benzodiazepin-2-(H)one (Ro5-3335) or 7-chloro-1,3-dihydro-5-(1H-pyrrol-2-yl)-3H-1,4-benzodiazepin-2-amine (Ro24-7429);
interferons, such as α -interferon; renal excretion
30 inhibitors such as probenecid; nucleoside transport inhibitors such as dipyrindamole; pentoxifylline; N-acetylcysteine (NAC); Procysteine; α -trichosanthin;

-388-

phosphonoformic acid; immunomodulators, such as interleukin II or thymosin; granulocyte macrophage colony stimulating factors; erythropoetin; soluble CD₄ and genetically engineered derivatives thereof; non-

5 nucleoside reverse transcriptase inhibitors (NNRTIs), such as nevirapine (BI-RG-587), zidovudine (ZDV) or didanosine (ddI); phosphonoformic acid; 1,4-dihydro-2H-3,1-benzoxazin-2-ones NNRTIs, such as (-)-6-chloro-4-cyclopropylethynyl-4-trifluoromethyl-1,4-dihydro-2H-3,1-

10 benzoxazin-2-one (L-743,726 or DMP-266); or quinoxaline NNRTIs, such as isopropyl (2S)-7-fluoro-3,4-dihydro-2-ethyl-3-oxo-1(2H)-quinoxalinecarboxylate (HBY1293), wherein said additional agent is administered to said patient as either a separate dosage form or as a single

15 dosage form together with said compound.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/15781

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C311/16 C07C311/29 C07D317/46 A61K31/36 A61P31/18
 A61K31/352 C07D493/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, CHEM ABS Data, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 843 946 A (MUELLER RICHARD A ET AL) 1 December 1998 (1998-12-01) cited in the application claim 5; table 1B ---	1-27
Y	US 5 744 481 A (MUELLER RICHARD A ET AL) 28 April 1998 (1998-04-28) cited in the application claim 1; table 11 ---	1-27
Y	WO 94 10136 A (SEARLE & CO ;MONSANTO CO (US); VAZQUEZ MICHAEL L (US); MUELLER RIC) 11 May 1994 (1994-05-11) claim 1; table 5 ---	1-27
	--- -/--	

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "&" document member of the same patent family

Date of the actual completion of the international search

5 October 2000

Date of mailing of the international search report

19 10 00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3016

Authorized officer

Härtinger, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/15781

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GHOSH A K ET AL: "Potent HIV protease inhibitors incorporating high-affinity P2-ligands and (R)-(hydroxyethylamino)sulfonamide isostere" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 8, no. 6, 17 March 1998 (1998-03-17), pages 687-690, XP004136945 ISSN: 0960-894X page 688, paragraph 1; table 1 -----	1-27
Y	FRESKOS J N ET AL: "(Hydroxyethyl) Sulfonamide HIV-1 Protease Inhibitors: Identification Of The 2-Methylbenzoyl Moiety At P-2" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS,GB,OXFORD, vol. 6, no. 4, 20 February 1996 (1996-02-20), pages 445-450, XP004135054 ISSN: 0960-894X page 445, paragraph 1; table 1 -----	1-27
A	EP 0 434 365 A (MERCK & CO INC) 26 June 1991 (1991-06-26) tables III,V -----	1-27
A	US 5 622 949 A (TALLEY JOHN J ET AL) 22 April 1997 (1997-04-22) column 60; table 4 -----	1-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/15781

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23 to 27 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.
2. ☒ Claims Nos.: 1-14 (part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-14 (part)

Present claims 1-14 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. In particular the group "Ht" is vague and open in that it embraces a vast number of carbocyclic and heterocyclic rings each being monocyclic or polycyclic, saturated or aromatic, substituted and/or fused to an enormous list of the same or further groups. The said group "Ht" also has been used to define the essential structural fragments of the claimed compounds (cf. A, D, D' and E). Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts which combine the technical features of claims 4 to 9, i.e. compounds of the formula II having R8 as defined in claim 4, R7 as defined in claim 5, A as defined in claim 6, D' as defined in claim 7, E as defined in claim 8 and D as defined in claim 9. All of the individualized and tested compounds of the invention fall under the above defined matter.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/15781

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5843946 A	01-12-1998	AT 174587 T	15-01-1999
		AU 7669794 A	21-03-1995
		DE 69415326 D	28-01-1999
		DE 69415326 T	02-06-1999
		EP 0715618 A	12-06-1996
		ES 2127938 T	01-05-1999
		GR 3029378 T	28-05-1999
		WO 9506030 A	02-03-1995
		US 5830897 A	03-11-1998
		US 5786483 A	28-07-1998
		US 5744481 A	28-04-1998
		AT 172717 T	15-11-1998
		AU 680635 B	07-08-1997
		AU 5347494 A	15-03-1994
		CA 2140929 A	26-02-1994
		DE 69321845 D	03-12-1998
		DE 69321845 T	29-04-1999
		EP 0656887 A	14-06-1995
		EP 0810209 A	03-12-1997
		ES 2123065 T	01-01-1999
		FI 950650 A	14-02-1995
		JP 8501288 T	13-02-1996
		NO 950533 A	13-02-1995
		NO 983099 A	13-02-1995
		WO 9404492 A	03-03-1994
		US 6060476 A	09-05-2000
		US 5968942 A	19-10-1999
		US 6046190 A	04-04-2000
US 5744481 A	28-04-1998	US 5843946 A	01-12-1998
		AT 174587 T	15-01-1999
		AU 7669794 A	21-03-1995
		DE 69415326 D	28-01-1999
		DE 69415326 T	02-06-1999
		EP 0715618 A	12-06-1996
		ES 2127938 T	01-05-1999
		GR 3029378 T	28-05-1999
		WO 9506030 A	02-03-1995
		US 5830897 A	03-11-1998
		US 5786483 A	28-07-1998
		AT 172717 T	15-11-1998
		AU 680635 B	07-08-1997
		AU 5347494 A	15-03-1994
		CA 2140929 A	26-02-1994
		DE 69321845 D	03-12-1998
		DE 69321845 T	29-04-1999
		EP 0656887 A	14-06-1995
		EP 0810209 A	03-12-1997
		ES 2123065 T	01-01-1999
		FI 950650 A	14-02-1995
		JP 8501288 T	13-02-1996
		NO 950533 A	13-02-1995
		NO 983099 A	13-02-1995
		WO 9404492 A	03-03-1994
		US 6060476 A	09-05-2000
		US 5968942 A	19-10-1999
		US 6046190 A	04-04-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/15781

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9410136 A	11-05-1994	AT 183499 T	15-09-1999
		AU 5665194 A	24-05-1994
		CA 2143191 A	11-05-1994
		DE 69326077 D	23-09-1999
		DE 69326077 T	27-01-2000
		EP 0666843 A	16-08-1995
		EP 0885881 A	23-12-1998
		EP 0885880 A	23-12-1998
		ES 2134924 T	16-10-1999
		US 5583132 A	10-12-1996
EP 0434365 A	26-06-1991	AU 6822990 A	27-06-1991
		CA 2032259 A	19-06-1991
		CN 1053607 A	07-08-1991
		FI 906212 A	19-06-1991
		JP 5345775 A	27-12-1993
		NO 905428 A	19-06-1991
		PT 96234 A	15-10-1991
		ZA 9010125 A	25-09-1991
US 5622949 A	22-04-1997	US 5475013 A	12-12-1995
		US 5620977 A	15-04-1997
		US 5698569 A	16-12-1997
		DE 69130070 D	01-10-1998
		DE 69130070 T	29-04-1999
		DK 558603 T	14-12-1998
		EP 0558603 A	08-09-1993
		JP 6502860 T	31-03-1994
		AT 170169 T	15-09-1998
		AT 155779 T	15-08-1997
		AT 164839 T	15-04-1998
		AT 147378 T	15-01-1997
		AT 136888 T	15-05-1996
		AU 9053191 A	11-06-1992
		AU 662114 B	24-08-1995
		AU 9085191 A	11-06-1992
		AU 661667 B	03-08-1995
		AU 9092591 A	11-06-1992
		AU 9125191 A	11-06-1992
		AU 662309 B	31-08-1995
		AU 9133291 A	11-06-1992
		CA 2096407 A	20-05-1992
		CA 2096409 A	20-05-1992
		CA 2096525 A	20-05-1992
		CA 2096528 A	20-05-1992
		DE 69118907 D	23-05-1996
		DE 69124110 D	20-02-1997
		DE 69126987 D	04-09-1997
		DE 69126987 T	05-03-1998
		DE 69129235 D	14-05-1998
		DE 69129235 T	12-11-1998
		DK 554400 T	16-02-1998
		DK 558630 T	11-05-1998
		DK 558657 T	07-07-1997
		DK 558673 T	29-07-1996
		EP 0554400 A	11-08-1993
		EP 0558630 A	08-09-1993
		EP 0558657 A	08-09-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/15781

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5622949 A		EP 0558673 A	08-09-1993
		EP 0735019 A	02-10-1996
		EP 0731088 A	11-09-1996
		EP 0813867 A	29-12-1997
		EP 0815856 A	07-01-1998
		EP 0813868 A	29-12-1997
		ES 2059293 T	16-11-1994
		ES 2059289 T	16-11-1994
		ES 2059295 T	16-11-1994
		ES 2059294 T	16-11-1994
<hr/>			